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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number
WO 02/28882 A1

(51) International Patent Classification[7]: C07J 9/00, 41/00, A61K 31/56

(21) International Application Number: PCT/US01/31394

(22) International Filing Date: 5 October 2001 (05.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/238,758	6 October 2000 (06.10.2000)	US
60/297,654	11 June 2001 (11.06.2001)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:

US	60/238,758 (CON)
Filed on	6 October 2000 (06.10.2000)

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/28882 A1

(54) Title: BILE ACID PRODRUGS OF L-DOPA AND THEIR USE IN THE SUSTAINED TREATMENT OF PARKINSONISM

(57) Abstract: Bile-acid conjugates useful for sustained release of L-DOPA, inhibitors of catechol O-methyl transferase and/or inhibitors of L-aromatic amino acid decarboxylase are provided.

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reaches the systemic circulation after oral administration. The absolute bioavailability of levodopa is dose-dependent, due to saturation of the active transport pathway.[1] Plasma levels of levodopa must be carefully titrated for each patient to achieve the optimal therapeutic activity. If the concentration of levodopa is too low in plasma (and consequently in the brain), the patient may experience a return of the symptoms of Parkinson's disease (rigidity, tremor, bradykinesia, etc.). If plasma drug levels are too high, toxic side effects may occur. Uncontrolled fluctuations in plasma levodopa levels may greatly contribute to the incidence of "on-off" fluctuations (dyskinesias). The most effective control of Parkinsonism is observed when plasma levels of levodopa are maintained in a narrow range, for example, by continuous intraduodenal infusion[10].

Following absorption, levodopa is rapidly converted to dopamine by L-aromatic amino acid decarboxylase (AADC) in the intestines and the liver. It has been shown that intestinal metabolism of levodopa is the major source of first pass loss of the drug. Intraportal and intravenous administration gave similar levodopa systemic exposures in rats.[8] In patients, less than 1% of the administered dose reaches the CNS intact, following transport across the blood-brain barrier by the neutral amino acid transporter. For this reason, levodopa is normally coadministered with a drug designed to inhibit its peripheral decarboxylation (e.g., carbidopa or benserazide). When administered with carbidopa, intact levodopa is transported into the CNS where it can be converted to dopamine. Carbidopa itself does not cross the blood-brain barrier and, therefore, does not inhibit the required conversion of levodopa to dopamine in the brain.

The oral bioavailability of levodopa from conventional formulations of levodopa/carbidopa (e.g. Sinemet) is 84-99%.[14,17] The half-life of levodopa in the plasma of patients is about 50 minutes when administered alone, or 1 to 2 hours when coadministered with carbidopa. For this reason,

the brain and can competitively inhibit uptake of levodopa from plasma to brain.[2] The nitrocatechol compounds entacapone, nitecapone and tolcapone are selective COMT inhibitors that are used clinically to block the peripheral O-methylation of levodopa. These compounds produce a significant (up to 50%) increase in half-life and the area-under-the curve (AUC) of levodopa when used as an adjunct to levodopa-carbidopa regimens.

The potential use of various simple esters as prodrugs of levodopa as a means to improve the pharmacokinetics of the drug has been proposed.[3,9,18-22,23] An oral formulation of levodopa methyl ester (Levomet, CHF 1301) has been described (Chiesi Pharmaceuticals). The ethyl ester of levodopa (TV-1203) is under clinical investigation as a potential therapy for Parkinsonism when coadministered with carbidopa.[26] A sustained release formulation of levodopa ethyl ester in a mixture of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and a carboxyvinyl polymer has been described.[27] However, oral administration of this formulation to healthy adults pretreated with carbidopa produced a plasma levodopa terminal half-life of only 2 hours; comparable to that of Sinemet CR. This result indicates that the ester was absorbed faster than the rate of its hydrolysis to levodopa. A pivaloyl ester of levodopa (NB-355) has been described.[21] Conversion of the prodrug to levodopa in rat plasma following absorption from an intestinal loop was slow and sustained levels of prodrug were observed, while levels of levodopa were low. The potential for using ester prodrugs of levodopa to enhance rectal absorption of the drug has been described.[19,20,22] Notably, the absorption of simple alkyl esters of levodopa has been shown to be greater following rectal absorption than following oral dosing.[6,7] This effect is due to the decreased abundance of esterases in the large intestine relative to the small intestine. Therefore, selective delivery of a prodrug of levodopa to the large intestine in a sustained release formulation would be expected to provide a greater oral biovailability and a prolonged exposure to the drug.

< 50%) of the prodrug is cleaved during each pass through the enterohepatic cycle. Thus, the enterohepatic circulation serves as a reservoir of the drug enabling sustained systemic drug levels to be achieved. One aspect of the present invention is related to prodrugs of levodopa, the AACD inhibitor and/or COMT inhibitor that can provide sustained release of levodopa, the AACD inhibitor and/or COMT inhibitor in a mammalian patient after oral administration of the prodrug.

For anti-Parkinson therapy, it may be advantageous to coadminister to patients recirculating prodrugs of levodopa together with similar prodrugs of AACD and/or COMT inhibitors. In this manner, one can sustain the level of levodopa in the peripheral circulation ensuring that therapeutic drug levels can be sustained within the brain. Another aspect of the present invention is related to prodrugs of levodopa and the AACD inhibitor or prodrugs of levodopa and the COMT inhibitor that can provide sustained release of levodopa and the AACD inhibitor or COMT inhibitor in a mammalian patient after oral administration of the prodrug.

Preferred prodrugs of this invention are bile acid conjugates of the aforementioned drugs. Naturally occurring bile acids such as cholic acid, chenodeoxycholic acid, ursodeoxycholic acid, deoxycholic acid, ursocholic acid and lithocholic acid are particularly preferred. The site of conjugation of these bile acids to the drugs is preferably via the 3-hydroxy group or the C-24 carboxyl moiety, as illustrated in Figure. 1. Optionally, a cleavable linker functionality (Y or Y' in formula (I) below) may be introduced between the drug and the bile acid and this linker may be selected such that its rate of cleavage *in vivo* is optimized to produce the desired degree of sustained systemic exposure to the drug.

In one embodiment this invention is directed to prodrugs of the formula D-Y-T, wherein D represents bile acid conjugates of the

–M–Y'–D'

where:

M is selected from the group consisting of $–CH_2OC(O)–$ and $–CH_2CH_2C(O)–$;

Y' is a covalent bond or a cleavable linker group covalently connecting D' to M;

D' is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

with the proviso that either X is -Y-D and/or W is –M–Y'–D'

wherein the compound of formula (I) above is a substrate for an intestinal bile acid transporter;

or a pharmaceutically acceptable salt thereof.

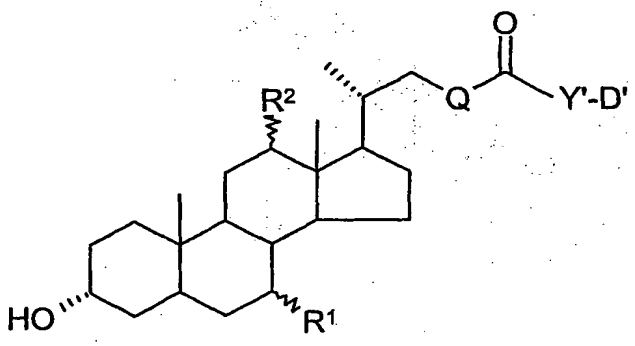
The linker groups Y and Y' are more preferably represented by the formula $–X^*-Y^*-Z-$ where X^* is the linker chemistry for attachment to the drug D or D'; Y^* is a covalent bond or a linker moiety; and Z is the linker chemistry for attachment to the steroid.

Preferably X^* is selected from the group consisting of $-\underline{O}C(O)-$, $-\underline{O}C(O)NR^7-$, $-\underline{O}C(O)OCR^{11}R^{12}O-$, $-\underline{O}C(O)OCR^{11}R^{12}OC(O)-$, $-\underline{O}C(O)OCR^{11}R^{12}OC(O)O-$, $-\underline{O}C(O)OCR^{11}R^{12}OC(O)NR^7-$, $-\underline{N}R^7C(O)O-$, $-\underline{N}R^7C(O)-$, $-\underline{N}R^7C(O)OCR^{11}R^{12}OC(O)-$, $-\underline{N}R^7C(O)OCR^{11}R^{12}OC(O)O-$, $-\underline{N}R^7CH_2NR^7C(O)-$, $-\underline{C}(O)O-$, $-\underline{C}(O)S-$, $-\underline{C}(O)NR^7-$, $-\underline{C}(O)NR^7C(O)R^7-$, $-\underline{C}(O)OCR^{11}R^{12}O-$, $-\underline{C}(O)OCR^{11}R^{12}OC(O)-$, $-\underline{C}(O)OCR^{11}R^{12}OC(O)O-$, $-\underline{C}(O)OCH_2C(O)NR^7-$, $-\underline{C}(O)OCH_2CH_2NR^7C(O)-$, $-\underline{C}(O)OCH_2NR^7C(O)-$, $-\underline{C}(O)OCR^{11}R^{12}OC(O)NR^7-$, with the underlined atom being derived from a hydroxyl, NH, or carboxylic acid moiety of the drug D or D';

each R^7 is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted

substituted arylene, heteroarylene, substituted heteroarylene, heterocyclene and substituted heterocyclene; and each of f, g and h are independently an integer from 0 to 3. More preferably, Y^* is alkylene, alkenylene or alkynylene.

One preferred group of prodrugs of the present invention are compounds represented by formula (I-a):



(I-a)

wherein:

Y' is selected from the group consisting of a covalent bond and a cleavable linker group covalently connecting D' to the C-24 position of the steroid;

D' is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

Q is CH_2 or O;

R^1 is selected from the group consisting of H and OH;

R^2 is selected from the group consisting of H and OH;

wherein the compound of formula (I-a) above is a substrate for an intestinal bile acid

transporter; or

pharmaceutically acceptable salts thereof.

V and V* are independently NR^7, O, S or CR^8R^9;

U is NR^7, O, S;

R^{10} is R^8 or $(CR^8R^9)_rT$;

T is selected from the group consisting of CO_2H, SO_3H, OSO_3H, SO_2H, $P(O)(OR^6)(OH)$, $OP(O)(OR^6)(OH)$ and pharmaceutically acceptable salts thereof;

each m is 0 or 1;

n' is 0, 1, 2, 3 or 4;

p is 0, 1,2 ,3 ,4, 5, or 6;

each q is independently 1, 2, 3, 4, 5, or 6;

r is 0 or 1;

R^6 is selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl;

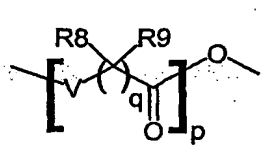
R^7, R^8 and R^9 are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^8 and R^9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring, or, when R^7 and R^9 are present and attached to adjacent atoms, then R^7 and R^9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring;

R^{11} and R^{12} are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{11} and R^{12} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring;

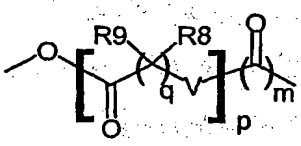
wherein the compound of formula (I-b) above is a substrate for an intestinal bile acid transporter;

or pharmaceutically acceptable salts thereof.

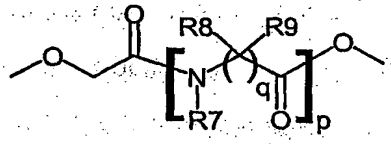
Particularly preferred examples of suitable cleavable linkers Y for use in formula (I-b) include structures of formulae (i) through (v) as shown below;



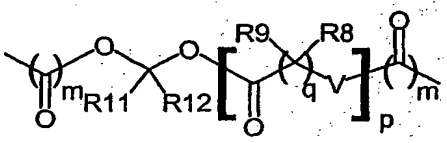
(i)



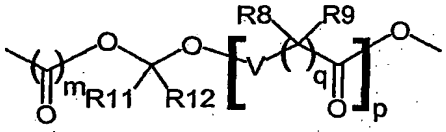
(ii)



(iii)



(iv)



(v)

wherein

V is selected from the group consisting of NR^7, O, S and CR^8R^9;

each m is independently 0 or 1;

p is 0, 1,2 ,3 ,4, 5, or 6;

each q is independently 1, 2, 3, 4, 5 or 6;

each R^7, R^8 and R^9 is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^8 and R^9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring, or, when R^7 and R^9 are present

Y is selected from the group consisting of a covalent bond and a cleavable linker group covalently connecting D to the steroid;

D is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

Q is CH_2 or O;

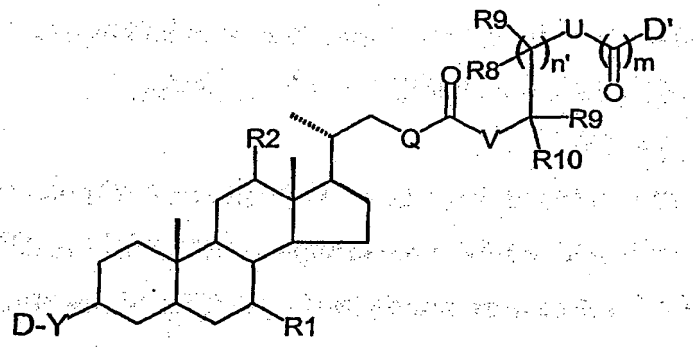
R^1 is selected from the group consisting of H and OH;

R^2 is selected from the group consisting of H and OH;

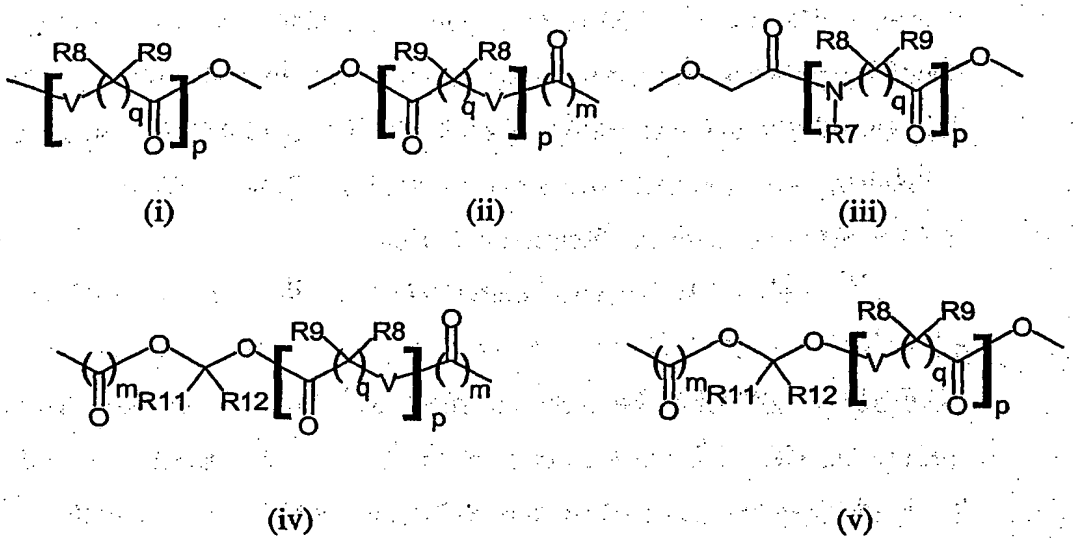
wherein the compound of formula (I-c) above is a substrate for an intestinal bile acid transporter;

and pharmaceutically acceptable salts thereof.

Particularly preferred prodrugs of formula (I-c) are compounds represented by formulae (I-c-1) and (I-c-2):



(I-c-1)



(i) (ii) (iii)

(iv) (v)

wherein

each V and V* are independently NR^7, O, S or CR^8R^9;

U is NR^7, O, S;

R^{10} is R^8 or $(CR^8R^9)_rT$;

T is selected from the group consisting of CO_2H, SO_3H, OSO_3H, SO_2H, $P(O)(OR^6)(OH)$, $OP(O)(OR^6)(OH)$ and pharmaceutically acceptable salts thereof;

each m is 0 or 1;

n' is 0, 1, 2, 3 or 4;

p is 0, 1,2 ,3 ,4, 5, or 6;

each q is independently 1, 2, 3, 4, 5, or 6;

r is 0 or 1;

R^6 is selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl;

R^7, R^8 and R^9 are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^8 and R^9 together with the atoms

Figure 2 illustrates catechol protection strategies applicable to L-DOPA and carbidopa bile acid conjugates.

Figure 3 illustrates multi-drug bile acid conjugates for sustained release of L-DOPA, wherein Y and Y' are optional linker groups, D and D' are independently L-DOPA, carbidopa, benserazide, entacapone, nitecapone and tolcapone, but at least one of D and D' is L-DOPA.

Figures 4-10 illustrate bile acid conjugates for sustained release of L-DOPA.

Figures 11-18 illustrate bile acid conjugates for sustained release of carbidopa.

Figures 19-23 illustrate bile acid conjugates for sustained release of benerazide.

Figures 24 and 25 illustrate bile acid conjugates for sustained release of the COMT inhibitors.

Figures 26-28 illustrate a method of preparing some intermediates for the preparation of some of the compounds of formula (I).

Figures 29-31 illustrate the preparation of some of the compounds of formula (I) where D is L-DOPA or carbidopa with D linked to Y via an ester linkage obtained via a reaction of the carboxyl group of L-DOPA or carbidopa.

Figure 32 illustrates a method for preparing some of the compounds of formula (I) where D is L-DOPA or carbidopa with D linked to Y via an amide linkage obtained via a reaction of the carboxyl group of L-DOPA or carbidopa.

absorption across the intestinal epithelium and enterohepatic recirculation via active transport through the bile acid transport system. Cleavage of the drug from a portion of the total conjugate present during each cycle through the enterohepatic circulation provides for sustained release of the drug.

However, prior to describing this invention in further detail, the following terms will first be defined:

Definitions

As used herein, the term "translocation across the intestinal wall" refers to movement of a drug or drug conjugate by a passive or active mechanism, or both, across an epithelial cell membrane of any region of the gastrointestinal tract.

"Active metabolite of a drug" refers to products of *in vivo* modification of the compounds of this invention which have therapeutic or prophylactic effect.

"Therapeutic or prophylactic blood concentrations" refers to systemic exposure to a sufficient concentration of a drug or an active metabolite thereof over a sufficient period of time to effect disease therapy or to prevent the onset or reduce the severity of a disease in the treated animal.

"Sustained release" refers to release of a therapeutic or prophylactic amount of the drug or an active metabolite thereof into the systemic blood circulation over a prolonged period of time relative to that achieved by oral administration of a conventional formulation of the drug.

"Tissue of the enterohepatic circulation" refers to the blood, plasma, intestinal contents, intestinal cells, liver cells, biliary tract or any fraction, suspension, homogenate, extract or preparation thereof.

"Conjugating" refers to the formation of a covalent bond.

aromatic amino acid decarboxylase inhibitor is released. The cleavable linker preferably comprises one or more functional groups such as ester groups, amide groups, glycolamide ester groups, amidomethyl esters, acyloxyalkyl esters, alkoxycarbonyloxyalkyl esters, and the like.

"Derivatives of L-DOPA" preferably refers to L-DOPA molecules wherein:

a) a hydrogen atom of the amino group of the L-DOPA molecule is replaced with $-C(O)R^4$, $-C(O)OR^5$ or an amino acid group, wherein R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl and substituted heteroaryl, and R^5 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl and substituted heteroaryl; and/or

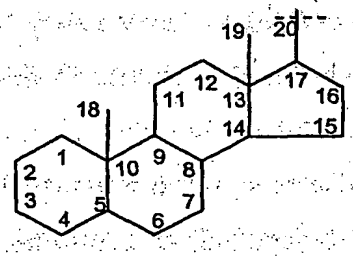
b) one or two hydrogen atoms of the two –OH groups of the catechol group of the L-DOPA molecule are replaced with $-C(O)R^4$, $-C(O)OR^5$ and/or $-OCR^3R^4OC(O)R^5$ wherein R^5 is defined as above, R^3 and R^4 independently are members selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl and substituted heteroaryl, or R^3 and R^4 together with the carbon atom to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring, or the two –OH groups of the catechol group of the L-DOPA molecule are protected with a 5-membered cyclic carbonate or 2,3-dioxo-1,4-dioxane ortho fused with a benzene ring of the catechol group of the L-DOPA molecule; and/or

with the proviso that one of the amino hydrogen atoms, the hydroxyl group of the carboxyl moiety or the hydrogen atom of one of the hydroxyl groups of the catechol/pyrogallol is removed to form a covalent bond to Y or Y'.

"Catechol O-methyl transferase inhibitor" preferably refers to catechol O-methyl transferase inhibitors such as entacapone, nitecapone and tolcapone optionally with one or two hydrogen atoms of two hydroxyl groups of the catechol group replaced with $-C(O)R^4$, $-C(O)OR^5$ and/or $-OCR^3R^4OC(O)R^5$, wherein R^3 and R^4 independently are members selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl and substituted heteroaryl, or R^3 and R^4 together with the carbon atom to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring, R^5 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl and substituted heteroaryl, or the OH group of the carboxyl moiety is replaced by $-OR^4$

with the proviso that one of the amino hydrogen atoms or the hydrogen atom of one of the hydroxyl groups of the catechol is removed to form a covalent bond to Y or Y'.

"Steroid" or "sterol" refers to the following core structure with the appropriate numbering system inserted therein:



Accordingly, cholic acid which has the structure:

substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR where R is hydrogen or alkyl, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkyl/substituted alkyl groups substituted with -SO$_2$-alkyl, -SO$_2$-substituted alkyl, -SO$_2$-alkenyl, -SO$_2$-substituted alkenyl, -SO$_2$-cycloalkyl, -SO$_2$-substituted cycloalkyl, -SO$_2$-aryl, -SO$_2$-substituted aryl, -SO$_2$-heteroaryl, -SO$_2$-substituted heteroaryl, -SO$_2$-heterocyclic, -SO$_2$-substituted heterocyclic and -SO$_2$NRR where R is hydrogen or alkyl.

"Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Alkenyl" refers to alkenyl group preferably having from 2 to 20 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted

"Alkynyl" refers to alkynyl group preferably having from 2 to 20 carbon atoms and more preferably 3 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation.

"Substituted alkynyl" refers to alkynyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl,

carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted alkenyl groups having amino groups blocked by conventional

-OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR where R is hydrogen or alkyl, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted alkenyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups substituted with -SO$_2$-alkyl, -SO$_2$-substituted alkyl, -SO$_2$-alkenyl, -SO$_2$-substituted alkenyl, -SO$_2$-cycloalkyl, -SO$_2$-substituted cycloalkyl, -SO$_2$-aryl, -SO$_2$-substituted aryl, -SO$_2$-heteroaryl, -SO$_2$-substituted heteroaryl, -SO$_2$-heterocyclic, -SO$_2$-substituted heterocyclic and -SO$_2$NRR where R is hydrogen or alkyl.

"Alkynylene" refers to a divalent alkynylene group preferably having from 2 to 20 carbon atoms and more preferably 1 to 6 carbon atoms and having from 1 to 2 sites of alkynyl unsaturation. This term is exemplified by groups such as ethynylene, propynylene and the like.

arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted alkenyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic and $-SO_2NRR$ where R is hydrogen or alkyl.

"Amidino" refers to the group $H_2NC(=NH)$- and the term "alkylamidino" refers to compounds having 1 to 3 alkyl groups (e.g., alkylHNC(=NH)-).

"Thioamidino" refers to the group RSC(=NH)- where R is hydrogen or alkyl.

"Aminoacyl" refers to the groups -NRC(O)alkyl, -NRC(O)substituted alkyl, -NRC(O)cycloalkyl, -NRC(O)substituted cycloalkyl, -NRC(O)alkenyl, -NRC(O)substituted alkenyl, -NRC(O)alkynyl, -NRC(O)substituted alkynyl, -NRC(O)aryl, -NRC(O)substituted aryl, -NRC(O)heteroaryl, -NRC(O)substituted heteroaryl, -NRC(O)heterocyclic, and -NRC(O)substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonyloxy" refers to the groups -NRC(O)O-alkyl,

atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the groups -NRC(O)NRR, -NRC(O)NR-alkyl, -NRC(O)NR-substituted alkyl, -NRC(O)NR-alkenyl, -NRC(O)NR-substituted alkenyl, -NRC(O)NR-alkynyl, -NRC(O)NR-substituted alkynyl, -NRC(O)NR-aryl, -NRC(O)NR-substituted aryl, -NRC(O)NR-cycloalkyl, -NRC(O)NR-substituted cycloalkyl, -NRC(O)NR-heteroaryl, and -NRC(O)NR-substituted heteroaryl, -NRC(O)NR-heterocyclic, and -NRC(O)NR-substituted heterocyclic where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonylamino" refers to the groups -NRC(S)NRR, -NRC(S)NR-alkyl, -NRC(S)NR-substituted alkyl, -NRC(S)NR-alkenyl, -NRC(S)NR-substituted alkenyl, -NRC(S)NR-alkynyl, -NRC(S)NR-substituted alkynyl, -NRC(S)NR-aryl, -NRC(S)NR-substituted aryl, -NRC(S)NR-cycloalkyl, -NRC(S)NR-substituted cycloalkyl, -NRC(S)NR-heteroaryl, and -NRC(S)NR-substituted heteroaryl, -NRC(S)NR-heterocyclic, and -NRC(S)NR-substituted heterocyclic where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic

cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -S(O)$_2$-alkyl, -S(O)$_2$-substituted alkyl, -S(O)$_2$-cycloalkyl, -S(O)$_2$-substituted cycloalkyl, -S(O)$_2$-alkenyl, -S(O)$_2$-substituted alkenyl, -S(O)$_2$-aryl, -S(O)$_2$-substituted aryl, -S(O)$_2$-heteroaryl, -S(O)$_2$-substituted heteroaryl, -S(O)$_2$-heterocyclic, -S(O)$_2$-substituted heterocyclic, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR where R is hydrogen or alkyl, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO$_2$NRR where R is hydrogen or alkyl.

"Arylene" refers to a divalent unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenylene) or

-OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR where R is hydrogen or alkyl, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO$_2$NRR where R is hydrogen or alkyl.

"Aryloxy" refers to the group aryl-O- which includes, by way of example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Aryloxyaryl" refers to the group -aryl-O-aryl.

"Substituted aryloxyaryl" refers to aryloxyaryl groups substituted with from 1 to 3 substituents on either or both aryl rings selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino,

arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with $-SO_2NRR$ where R is hydrogen or alkyl.

"Alkaryl" refers to the groups –alkylene aryl and –subsituted alkylene aryl wherein alkylene, substituted alkylene and aryl are as defined herein and are exemplified by groups such as benzyl, phenethyl and the like.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 8 carbon atoms having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl and the like. Excluded from this definition are multi-ring alkyl groups such as adamantanyl, etc.

"Cycloalkenyl" refers to cyclic alkenyl groups of frm 3 to 8 carbon atoms having a single cyclic ring.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refers to an cycloalkyl or cycloalkenyl group, preferably of from 3 to 8 carbon atoms, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,

$-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic and $-SO_2NRR$ where R is hydrogen or alkyl.

"Cycloalkylene" refers to divalent cyclic alkylene groups of from 3 to 8 carbon atoms having a single cyclic ring including, by way of example, cyclopropylene, cyclobutylene, cyclopentylene, cyclooctylene and the like.

"Cycloalkenylene" refers to a divalent cyclic alkenylene groups of frm 3 to 8 carbon atoms having a single cyclic ring.

"Substituted cycloalkylene" and "substituted cycloalkenylene" refers to a cycloalkylene or cycloalkenylene group, preferably of from 3 to 8 carbon atoms, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic,

-NRC(=NR)NR-alkenyl, -NRC(=NR)NR-substituted alkenyl, -NRC(=NR)NR-alkynyl, -NRC(=NR)NR-substituted alkynyl, -NRC(=NR)NR-aryl, -NRC(=NR)NR-substituted aryl, -NRC(=NR)NR-cycloalkyl, -NRC(=NR)NR-heteroaryl, -NRC(=NR)NR-substituted heteroaryl, -NRC(=NR)NR-heterocyclic, and -NRC(=NR)NR-substituted heterocyclic where each R is independently hydrogen and alkyl as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"*N*,*N*-Dimethylcarbamyloxy" refers to the group -OC(O)N(CH_3)$_2$.

"Guanidinosulfone" refers to the groups -NRC(=NR)NRSO_2-alkyl, -NRC(=NR)NRSO_2-substituted alkyl, -NRC(=NR)NRSO_2-alkenyl, -NRC(=NR)NRSO_2-substituted alkenyl, -NRC(=NR)NRSO_2-alkynyl, -NRC(=NR)NRSO_2-substituted alkynyl, -NRC(=NR)NRSO_2-aryl, -NRC(=NR)NRSO_2-substituted aryl, -NRC(=NR)NRSO_2-cycloalkyl, -NRC(=NR)NRSO_2-substituted cycloalkyl, -NRC(=NR)NRSO_2-heteroaryl, and -NRC(=NR)NRSO_2-substituted heteroaryl, -NRC(=NR)NRSO_2-heterocyclic, and -NRC(=NR)NRSO_2-substituted heterocyclic where each R is independently hydrogen and alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is either chloro or bromo.

-S(O)$_2$-substituted heterocyclic, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR where R is hydrogen or alkyl, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$- substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO$_2$NRR where R is hydrogen or alkyl.

"Heteroarylene" refers to a divalent aromatic carbocyclic group of from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroarylene groups can have a single ring (e.g., pyridylene or furylene) or multiple condensed rings (e.g., indolizinylene or benzothienylene). Preferred heteroarylenes include pyridylene, pyrrolylene, indolylene and furylene.

-NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO$_2$NRR where R is hydrogen or alkyl.

"Heteroaryloxy" refers to the group -O-heteroaryl and "substituted heteroaryloxy" refers to the group -O-substituted heteroaryl.

"Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl.

"Substituted heterocyclic" refers to heterocycle groups which are substituted with from 1 to 3 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro,

and substituted alkynyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cycloalkyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, -SO_2-substituted heterocyclic and -SO_2NRR where R is hydrogen or alkyl.

Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidine, tetrahydrofuranyl, and the like.

"Heterocyclene" refers to a divalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl.

"Substituted heterocyclene" refers to heterocyclene groups which are substituted with from 1 to 3 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy,

heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkynyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cycloalkyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, -SO_2-substituted heterocyclic and -SO_2NRR where R is hydrogen or alkyl.

"Heterocyclyloxy" refers to the group -O-heterocyclic and "substituted heterocyclyloxy" refers to the group -O-substituted heterocyclic.

"Thiol" refers to the group -SH.

"Thioalkyl" refers to the group -S-alkyl.

"Substituted thioalkyl" refers to the group -S-substituted alkyl.

"Thiocycloalkyl" refers to the group -S-cycloalkyl.

"Substituted thiocycloalkyl" refers to the group -S-substituted cycloalkyl.

"Thioaryl" refers to the group -S-aryl and "substituted thioaryl" refers to the group -S-substituted aryl.

"Thioheteroaryl" refers to the group -S-heteroaryl and "substituted thioheteroaryl" refers to the group -S-substituted heteroaryl.

"Thioheterocyclic" refers to the group -S-heterocyclic and "substituted thioheterocyclic" refers to the group -S-substituted heterocyclic.

It is understood, of course, that combinations of substituents within the compounds of formula (i) above do not include any combination which is chemical impossible or non-feasible as would be appreciated by one skilled in the art.

"Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of formula (i) which salts are derived from a variety of organic and inorganic counter ions well known in the art and

R^1 is α-OH and R^2 is H;

R^1 is β-OH and R^2 is H;

R^1 is H and R^2 is α-OH;

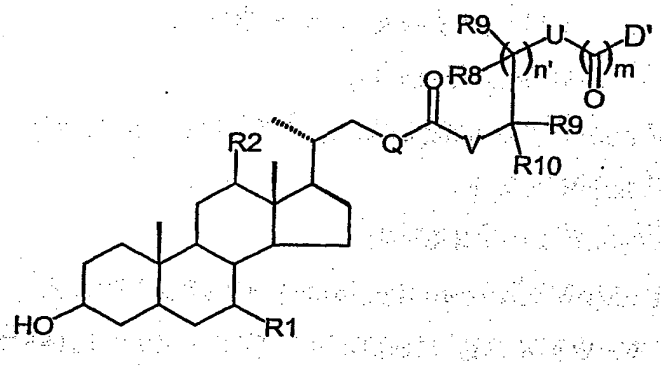
R^1 is β-OH and R^2 is α-OH; or

R^1 and R^2 are H;

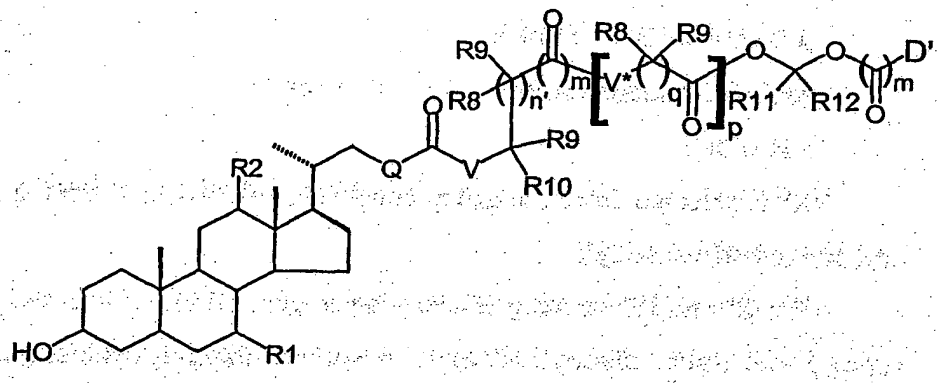
wherein the compound of formula (I-a) above is a substrate for an intestinal bile acid transporter;

or pharmaceutically acceptable salts thereof.

Particularly preferred prodrugs of formula (I-a) are compounds represented by formulae (I-a-1) and (I-a-2):



(I-a-1)



(I-a-2)

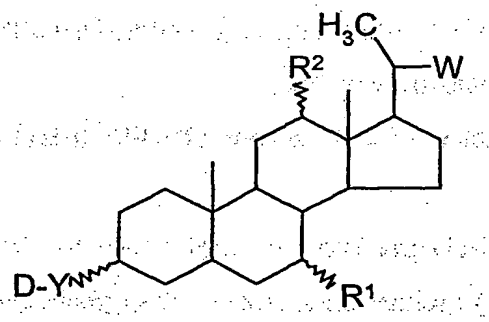
substituted aryl, heteroaryl, substituted heteroaryl or R^8 and R^9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring, or, when R^7 and R^9 are present and attached to adjacent atoms, then R^7 and R9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring;

R^{11} and R^{12} are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{11} and R^{12} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring;

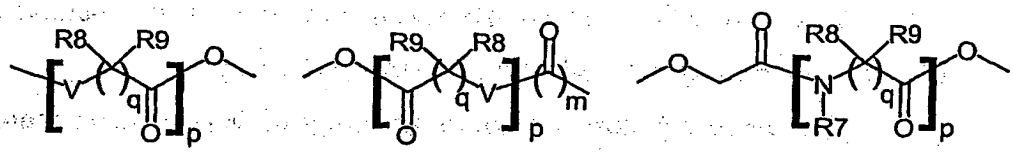
wherein the compound of formulae (I-a-1) and (I-a-2) above is a substrate for an intestinal bile acid transporter;

or pharmaceutically acceptable salts thereof.

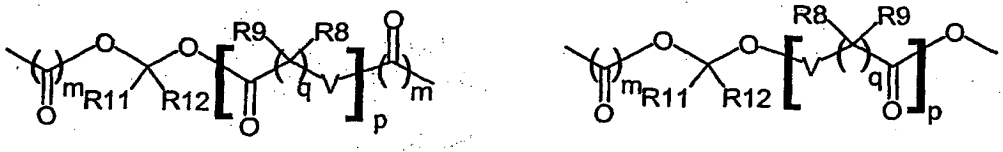
Another preferred group of prodrugs of the present invention are compounds represented by formula (I-b):



(I-b)



(i) (ii) (iii)



(iv) (v)

wherein

V is selected from the group consisting of NR^7, O, S and CR^8R^9;

each m is independently 0 or 1;

p is 0, 1,2 ,3 ,4, 5, or 6;

q is 1, 2, 3, 4, 5 or 6;

each R^7, R^8 and R^9 is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^8 and R^9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring, or, when R^7 and R^9 are present and attached to adjacent atoms, then R^7 and R^9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring;

R^{11} and R^{12} are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{11} and R^{12} together

R^1 and R^2 are one of the following combinations:

R^1 and R^2 are α-OH;

R^1 is α-OH and R^2 is H;

R^1 is β-OH and R^2 is H;

R^1 is H and R^2 is α-OH;

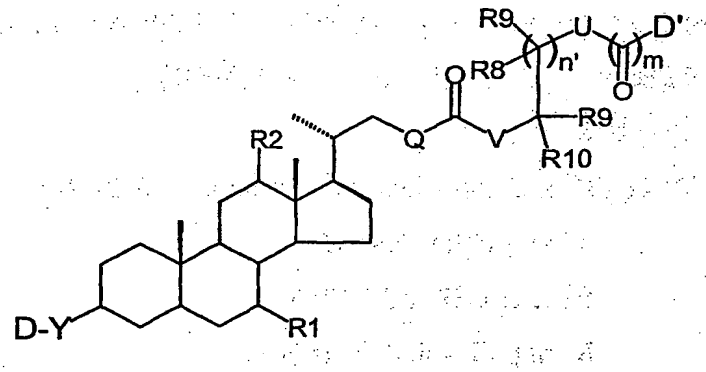
R^1 is β-OH and R^2 is α-OH; or

R^1 and R^2 are H;

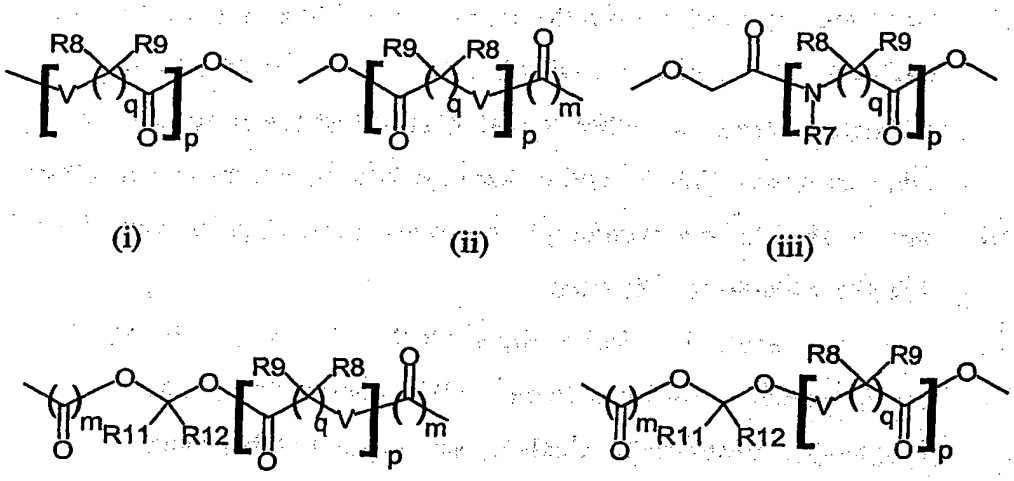
wherein the compound of formula (I-c) above is a substrate for an intestinal bile acid transporter;

or pharmaceutically acceptable salts thereof.

Particularly preferred prodrugs of formula (I-c) are compounds represented by formulae (I-c-1) and (I-c-2):



(I-c-1)



(i) (ii) (iii)

(iv) (v)

wherein

each V and V* are independently NR^7, O, S or CR^8R^9;

U is NR^7, O, S;

R^{10} is R^8 or $(CR^8R^9)_rT'$;

T' is selected from the group consisting of CO_2H, SO_3H, OSO_3H, SO_2H, $P(O)(OR^6)(OH)$, $OP(O)(OR^6)(OH)$ and pharmaceutically acceptable salts thereof;

each m is 0 or 1;

n' is 0, 1, 2, 3 or 4;

p is 0, 1,2 ,3 ,4, 5, or 6;

each q is independently 1, 2, 3, 4, 5, or 6;

r is 0 or 1;

R^6 is selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl;

R^7, R^8 and R^9 are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl

Also more preferably, in the compound of formula (I), X is –Y-D, D is L-DOPA or a derivative of L-DOPA, and W is –M–Y'–D' and D' is the catechol O-methyl transferase inhibitor.

Also more preferably, in the compound of formula (I), X is –Y-D, D is L-DOPA or a derivative of L-DOPA, and W is –M–Y'–D' where D' is the L-aromatic amino acid decarboxylase inhibitor.

The present invention also includes the compound of formula (I), wherein W is M–Y'-D' and D' is L-DOPA or a derivative of L-DOPA.

Preferably, in the compound of formula (I), W is –M–Y'–D' where D' is L-DOPA or a derivative of L-DOPA, X is –Y-D and D is L-DOPA, a derivative of L-DOPA, a catechol O-methyl transferase inhibitor, a L-aromatic amino acid decarboxylase inhibitor, or a pharmaceutically acceptable salt thereof.

Also preferably, in the compound of formula (I), W is –M–Y'–D' where D' is L-DOPA or a derivative of L-DOPA, X is –Y-D and D is a catechol O-methyl transferase inhibitor.

Additionally, it is preferred that, in the compound of formula (I), W is –M–Y'–D' where D' is L-DOPA or a derivative of L-DOPA, X is –Y-D and D is a L-aromatic amino acid decarboxylase inhibitor.

Another aspect of the present invention is directed to compounds of formula (I), wherein X is –Y-D and D is a catechol O-methyl transferase inhibitor. In these compounds, W is preferred to be –M–Y'–D' where D' is a catechol O-methyl transferase inhibitor or a L-aromatic amino acid decarboxylase inhibitor. These compounds are useful in the treatment of Parkinsonism when co-administered with L-DOPA or a prodrug of L-DOPA.

Another aspect of the present invention is directed to compounds of formula (I), wherein W is –M–Y'–D' where D' is a catechol O-methyl transferase inhibitor. In these compounds, X is preferred to be –Y-D,

transporters PEPT1 and PEPT2 localized in the intestine, kidney and brain. For dipeptide derivatives of levodopa, this may provide a higher capacity uptake pathway for delivery to the brain than the large neutral amino acid transporter utilized by levodopa itself. Note that it may not be desirable to induce transport of the AADC inhibitor carbidopa across the blood-brain barrier since it would block conversion of levodopa to dopamine within the CNS.

Also contemplated by this invention are prodrugs of formula (I) wherein X is Y-D and the carboxyl group (-COOH) of levodopa, a catechol O-methyl transferase inhibitor or a L-aromatic amino acid decarboxylase inhibitor is protected as an ester or an acyloxyalkyl ester.

One or more of the phenolic hydroxyl groups of these prodrugs may be protected via acylation or alkylation as illustrated in Figure 2. The corresponding ester, acyloxyalkyl ester or carbonate derivatives are hydrolyzed *in vivo* to regenerate the catechol moieties of the parent drugs. Such protection may be necessary, particularly for compounds having such phenolic hydroxyl groups in W, in order to permit the compounds of formula (i) to be a substrate for an intestinal bile acid transporter.

Within the scope of the present invention are bile acid prodrug derivatives that combine levodopa with one or more inhibitors of its metabolism (i.e., an AADC or COMT inhibitor). Some of these compounds are schematically represented in Figure 3. Such multi-drug bile acid analogs undergo enterohepatic circulation and hydrolysis *in vivo* to provide sustained systemic blood levels of both levodopa and the AADC or COMT inhibitor. Note that co-drug compositions are disclosed in U.S. Patent 6,051,576 and PCT Application WO95/20567, but active transport of such compounds by the bile acid transport system is not described therein. The present invention also includes prodrugs containing two or more units of levodopa. For example, when R^5 in compounds IV-IX and LXIII-LXVIII is

Q is CH_2 or O;

W is a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group consisting of –COOH, $-SO_3H$, $-SO_2H$, $-P(O)(OR^6)(OH)$, $-OP(O)(OR^6)(OH)$, $-OSO_3H$ and the like and pharmaceutically acceptable salts thereof, where R^6 is selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl;

R^1 and R^2 are one of the following combinations:

R^1 and R^2 are α-OH;

R^1 is α-OH and R^2 is H;

R^1 is β-OH and R^2 is H;

R^1 is H and R^2 is α-OH;

R^1 is β-OH and R^2 is α-OH; or

R^1 and R^2 are H;

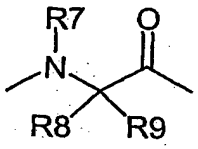
or a pharmaceutically acceptable salt thereof.

When Y and Y' are cleavable linker groups they are more preferably represented by the formula $–X^*-Y^*-Z-$ where X^* is the linker chemistry for attachment to the drug D or D'; Y^* is a covalent bond or a linker moiety; and Z is the linker chemistry for attachment to the steroid.

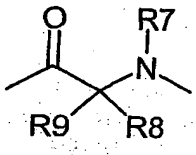
Preferably X^* is selected from the group consisting of $-\underline{O}C(O)-$, $-\underline{O}C(O)NR^7-$, $-\underline{O}C(O)OCR^{11}R^{12}O-$, $-\underline{O}C(O)OCR^{11}R^{12}OC(O)-$, $-\underline{O}C(O)OCR^{11}R^{12}OC(O)O-$, $-\underline{O}C(O)OCR^{11}R^{12}OC(O)NR^7-$, $-\underline{N}R^7C(O)O-$, $-\underline{N}R^7C(O)-$, $-\underline{N}R^7C(O)OCR^{11}R^{12}OC(O)-$, $-\underline{N}R^7C(O)OCR^{11}R^{12}OC(O)O-$, $-\underline{N}R^7CH_2NR^7C(O)-$, $-\underline{C}(O)O-$, $-\underline{C}(O)S-$, $-\underline{C}(O)NR^7-$, $-\underline{C}(O)NR^7C(O)R^7-$, $-\underline{C}(O)OCR^{11}R^{12}O-$, $-\underline{C}(O)OCR^{11}R^{12}OC(O)-$, $-\underline{C}(O)OCR^{11}R^{12}OC(O)O-$, $-\underline{C}(O)OCH_2C(O)NR^7-$, $-\underline{C}(O)OCH_2CH_2NR^7C(O)-$, $-\underline{C}(O)OCH_2NR^7C(O)-$, $-\underline{C}(O)OCR^{11}R^{12}OC(O)NR^7-$, with the underlined atom being derived from a hydroxyl, NH, carboxylic acid moiety of the drug D or D';

alkenylene, alkynylene, substituted alkynylene, cycloalkylene, substituted cycloalkylene, cycloalkenylene, substituted cycloalkenylene, arylene, substituted arylene, heteroarylene, substituted heteroarylene, heterocyclene and substituted heterocyclene; and each of f, g and h are independently an integer from 0 to 3. More preferably, Y^* is alkylene, alkenylene or alkynylene.

Examples of Y and Y′ are members selected from the group consisting of a carbonyl group, thiocarbonyl group and radicals of formulae (vi) to (xlviii):



(vi)



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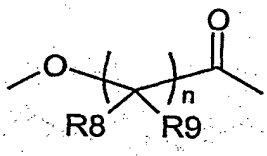

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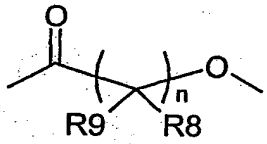

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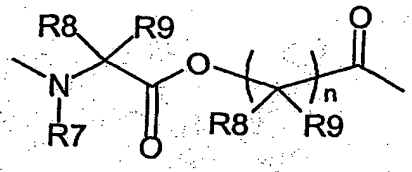

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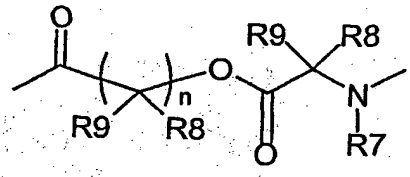

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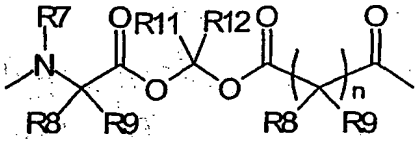
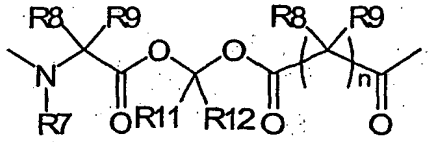


(xxii)



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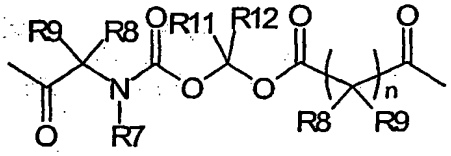

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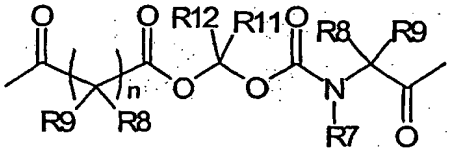

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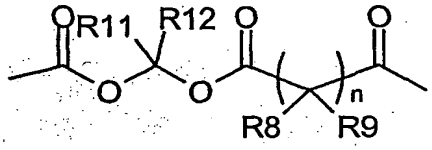

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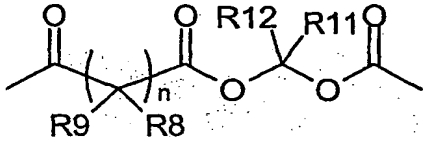

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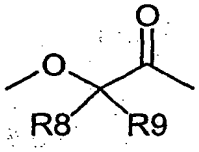

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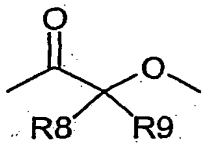

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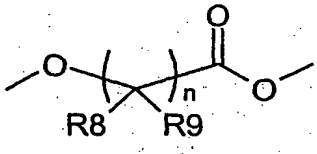

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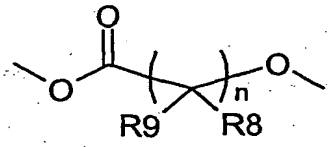

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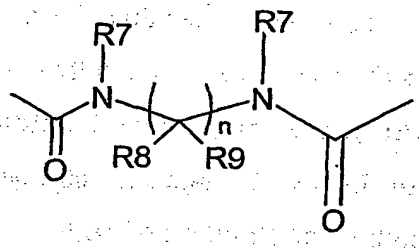

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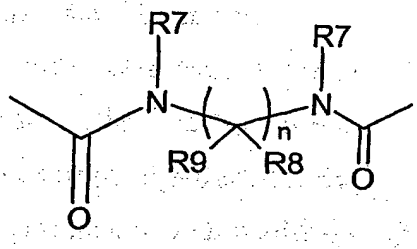

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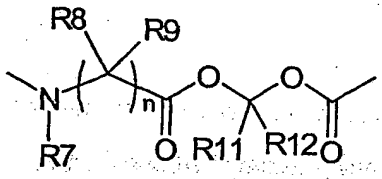

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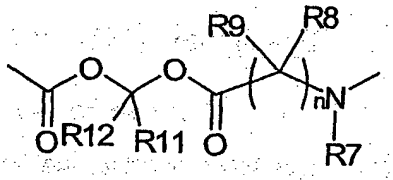

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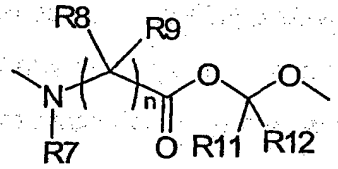

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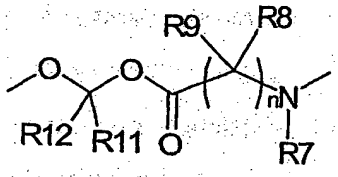


(xlvii)

wherein:

n is an integer of 1 to 6;

each R^7, R^8 and R^9 are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^8 and R^9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring, or, when R^7 and R^9 are present and attached to adjacent atoms, then R^7 and R^9 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring;

unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

Prodrugs of this invention may be prepared by methods well known in the art.[5,11,12,16,23, 25] The disclosures of these references are herein incorporated by reference. Some of the preparative methods can be found in U.S. Provisional Application No. 60\238758.[30]

The compounds of formula (I) above can be prepared by covalent coupling a difunctionalized linker precursor with a drug and a suitable transporter compound. The linker precursor is selected to contain at least one reactive functionality that is complementary to at least one reactive functionality on the drug and at least one reactive functionality on the transporter compound. Such complementary reactive groups are well known in the art as illustrated below:

COMPLEMENTARY BINDING CHEMISTRIES

First Reactive Group	Second Reactive Group	Linkage
hydroxyl	carboxylic acid	ester
amine	carboxylic acid	amide
hydroxyl	isocyanate	urethane
amine	epoxide	hydroxylamine
sulfonyl halide	amine	sulfonamide
hydroxyl	alkyl/aryl halide	ether
aldehyde	amine/$NaCNBH_4$	amine
ketone	amine/$NaCNBH_4$	amine
amine	isocyanate	urea

Suitable linker precursors include, by way of example, dicarboxylic acids, disulfonylhalides, dialdehydes, diketones, dihalides,

involves a reaction of a bile acid derivative, **CCCIII**, having a 3-α-OH group with formic acid, DEAD, i.e. diethyl azodicarboxylate, and triphenyl phosphine, followed by a reaction with KOH in methanol to generate an intermediate, **CCCIV**, which is reacted with methanesulfonyl chloride and then with a diol to obtain an intermediate, **CCCV**.

A method of preparing some bile acid intermediates, in which Y is $-O(CH_2)_nO-$, with n being an integer of 1 to 17 and W is $CH_2CH_2C(O)O^tBu$ is shown in Figure 28. The method involves first a protection of a terminal hydroxyl group attached to position 3 with TBDMS, i.e. t-butyldimethylsilyl, protection of the C-24 carboxyl group as a t-butyl ester, and then removal of TBDMS to obtain a hydroxyl intermediate, **CCCX** or **CCCXI**.

There are several methods for the preparation of some of the compounds of formula (I) where W is $CH_2CH_2CO_2H$, X is –Y-D, and D is L-DOPA or carbidopa by relying on the carboxyl group of L-DOPA and carbidopa to form an ester linkage with Y (see Figures 29-31). As shown in Figure 29, the first method involves a reaction of the hydroxyl intermediate, **CCCX** or **CCCXI**, with L-DOPA or carbidopa with an amino group protected with Cbz, i.e. benzyloxycarbonyl, followed by the removal of the t-butyl group and then the removal of the Cbz group, to obtain compound **CCCXII** or **CCCXIII**. In the second method (Figure 30), the intermediate, **CCCVIII** or **CCCIX**, is subjected to a series of reactions with acetic anhydride, TBAF, i.e. tetrabutylammonium fluoride, PDC, i.e. pyridinium dichromate and KOH to form an intermediate, **CCCXIV** or **CCCXV**, having a terminal carboxyl group at position 3. The intermediate, **CCCXIV** or **CCCXV**, is then converted to an iodomethyl ester, **CCCXVI** or **CCCXVII**, in a series of reactions involving chloroiodomethane and NaI. The iodomethyl ester is then reacted with the carboxyl group of an amino-protected L-DOPA or carbidopa followed by the removal of the *t*-butyl group and Cbz group to form a compound, **CCCXVIII** or **CCCXIX**, of

CCCXXVIII or CCCXXIX, by bromoacetic anhydride. A nucleophilic substitution is carried out with the amino group of L-DOPA, carbidopa or benserazide as a nucleophile and the bromo group of the bromoacetic intermediate, CCCXXVIII or CCCXXIX, as a leaving group to obtain a compound, CCCXXX or CCCXXXI, of formula (I). In the method of Figure 34, a carboxyl-protected intermediate, CCCXXXII or CCCXXXIII, is reacted with succinic anhydride to obtain an intermediate, CCCXXXIV or CCCXXXV, having a terminal carboxyl group at position 3. The carboxyl group of intermediate, CCCXXXIV or CCCXXXV, is reacted with the amino group of L-DOPA, carbidopa or benserazide using diisopropyl-carbodiimide, followed by the removal of the carboxyl protective group at position 17 to yield a compound, CCCXXXVI or CCCXXXVII, of formula (I) where D is attached to Y via an amide linkage. The method of Figure 35 is similar to the method of Figure 34 except that the method of Figure 35 (1) converts the 3-hydroxyl group of intermediate CCCXXXII or CCCXXXIII, to a 3-amino group using $(PhO)_2P(O)N_3$ and triphenyl phosphine and (2) uses 2,6-dicarbonyl-1,4-dioxane instead of succinic anhydride to generate an intermediate having a terminal carboxyl group at position 3.

Figures 36 and 37 illustrate two methods for preparing some of the compounds of formula (I) where W is $CH_2CH_2CO_2H$, X is –Y-D, and D is L-DOPA, carbidopa, benserazide, entacapone, nitecapone or tolcapone, with D linked to Y via an ester linkage obtained by a reaction of a hydroxyl group of D with a bile acid intermediate having a terminal carboxyl group at position 3. The bile acid intermediate, CCCXXXIV, CCCXXXV, CCCXXXVIII or CCCXXXIX, having a terminal carboxyl group at position 3 is prepared from intermediate CCCXXXII or CCCXXXIII using succinic anhydride in the method of Figure 36 or 2,6-dicarbonyl-1,4-dioxane in the method of Figure 37. The terminal carboxyl group at position 3 of the bile acid intermediate, CCCXXXIV, CCCXXXV, CCCXL or CCCXLI, is

administered by oral routes. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions that contain, as the active ingredient, one or more of the compounds of this invention associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, etc. containing, for example, up to 90% by weight of the active compound using, for example, soft and hard gelatin capsules.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. ~40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-

prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

EXAMPLES

In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

ATCC	=	American Type Tissue Culture
CHO	=	Chinese hampster ovary
CPM	=	counts per minute
DMEM	=	Dulbecco's minimum eagle medium

To an ice-cold solution containing cholic acid (816 mg, 2 mmol) and triethylamine (0.556 mL, 4 mmol) in anhydrous THF (100 mL) was added ethyl chloroformate (0.211 mL, 2.2 mmol). The reaction mixture was stirred at 0°C for 30 min. A solution of L-DOPA (788 mg, 4 mmol) and $NaHCO_3$ (420 mg, 5 mmol) in water (10 mL) was added at 0°C, then stirred for 30 min. at 0°C, and for a further 30 min. at room temperature. After removal of THF *in vacuo*, aqueous citric acid (20 mL) was added. The product was extracted with ethyl acetate (3 x 30 mL) and the combined organic phase was dried over $MgSO_4$ and concentrated to dryness. Chromatography on a silica gel column eluting with 5% MeOH/EtOAc gave the desired Cholyl-DOPA product (**101**) (880 mg, 75%). MS (ESI) *m/z* 588.33 ($M+H^+$).

^1H NMR (CD_3OD, 400 MHz, characteristic resonances only): 6.64 (d, 1H, J=8Hz), 6.64 (d, 1H, J=2Hz), 6.52 (dd, 1H, J=2Hz, J=8Hz), 4.56 (m, 1H), 3.06-2.75 (m, 2H), 0.98 (d, 3H, J=6.4Hz), 0.91 (s, 3H), 0.68 (s, 3H).

EXAMPLE 2

Synthesis of Cholyl-Dopa-(3,4-carbonate) (**104**)

Cholyl-DOPA (59 mg, 0.1 mmol) was dissolved in anhydrous THF (30 mL), 1, 1'-carbonyldiimidazole (32 mg, 0.2 mmol) was added and the mixture heated under reflux for 24 h. The reaction was monitored to completion by TLC (10% MeOH/EtOAc). After removal of the solvent *in vacuo*, the residue was dissolved in EtOAc, and washed with aqueous citric acid. The organic phase was dried over $MgSO_4$ and concentrated to dryness. Chromatography on a silica gel column eluting with 5% MeOH/EtOAc gave the desired cyclic carbonate product (**104**) (15 mg, 24%).

MS (ESI) *m/z* 614.38 ($M+H^+$).

stirred at room temperature for 15 min. Bromomethylacetate (155 μL, 1.5 mmol) was added and the mixture heated in an oil bath at 70°C for 18 h. The reaction was monitored to completion by TLC (10% MeOH/EtOAc). After removal of the solvent *in vacuo*, the residue was dissolved in EtOAc and washed with aqueous citric acid. The organic phase was dried over $MgSO_4$ and concentrated to dryness. Chromatography on a silica gel column eluting with 2% MeOH/EtOAc gave the desired product Cholyl-DOPA-(4-acetoxymethyl) (**103**) (240 mg, 36%). MS (ESI) *m/z* 660.22 ($M+H^+$). ^1H NMR (CD_3OD, 400 MHz, characteristic resonances only): 6.66 (d, 1H, J=8Hz), 6.63 (d, 1H, J=2Hz), 6.51 (dd, 1H, J=2Hz, J=8Hz), 5.72 (dd, 2H, J=2.8Hz, J=15.2Hz), 4.56 (m,1H), 3.02-2.75 (m, 2H), 2.06 (s, 3H), 0.98 (d, 3H, J=6.4Hz), 0.90 (s, 3H), 0.68 (s, 3H).

EXAMPLE 5

In Vitro Compound Transport Assays with IBAT and LBAT-Expressing Cell Lines

(a) Inhibition of Radiolabeled Taurocholate Uptake

CHO cells transfected with the IBAT or LBAT transporter were seeded into 96-well microtiter plates at 100,000 cells/well in 100 μL DMEM containing 10% serum, glutamine and Penstrep. After overnight incubation the media was removed and test compound (25 μL) added at 2x the final desired concentration. Tritiated taurocholate (50,000 CPM/well) was diluted with cold substrate to a final concentration of 5 μM and 25 μL/well of this mixture was added to the plate. After incubating for 1 h at room temperature the solution was removed and the plate washed 4x with PBS at 4°C. 200 μL/well of scintillant is added and the plate then read in a Wallac microbeta counter. The inhibition data is processed by standard methods to calculate an inhibition constant K_i for the test compound.

solutions were frog ringers solution containing $CaCl_2$. Drugs were applied for 10-30 seconds until the induced current reached a new steady-state level, followed by a control solution until baseline currents returned to levels that preceded drug application. The difference current (baseline subtracted from peak current during drug application) reflected the net movement of charge resulting from electrogenic transport and was directly proportional to tranport rate. Recordings were made from a single oocyte for up to 60 min, enabling 30-40 separate compounds to be tested per oocyte. Compound-induced currents were saturable and gave half-maximal values at substrate concentrations comparable to radiolabel competition experiments. To compare results between oocytes expressing different levels of transport activity, a saturating concentration of glycodeoxycholate (300 μM) was used as a common reference to normalize results from test compounds. Using this normalization procedure V_{max} (i.e. maximal induced current) for different compounds tested on different oocytes could be compared.

Table 1: *In vitro* transport data for selected compounds on IBAT-expressing cells

COMPOUND	IC_{50} (μM)	% Max. (GDC)
(101)	83	0
(104)	74	25
(102)	91	104

IC_{50} data from radiolabeled competition assay in transporter-expressing CHO cells

%Max response (relative to glycodeoxycholate) at a test compound concentration of 100 μM in transporter-expressing oocytes

Table 3. *In Vitro* Enzymatic Release of L-DOPA or (101) from (102)

Preparation	Substrate Concentration	Cofactors	Percent of L-Dopa Released in 60 min	Percent of (101) Released in 60 min*
Rat Plasma	2.0 μM	None	NR	75
Human Plasma	2.0 μM	None	NR	90
Rat Liver S9 (0.5 mg/mL)	2.0 μM	NADPH	NR	35
Human Liver S9 (0.5 mg/mL)	2.0 μM	NADPH	NR	70
Human Intestine S9 (0.5 mg/mL)	2.0 μM	NADPH	NR	95
Cholylglycine Hydrolase (87 units/mL)	0.8 μM	None	NR	NR

NR – Not released

* - XP11215 was further hydrolysed *in vitro* by cholylglycine hydrolase (95% in 60 min) to release L-Dopa.

EXAMPLE 7

Oral Bioavailability of L-DOPA and (101) from the Prodrug (102)

The pharmacokinetics of the prodrug (102) were examined in rats. Three groups of four male Sprague-Dawley rats (200-300 g) with jugular cannulae each received one of the following treatments: A) a single bolus intravenous injection of L-DOPA (75 mg/kg, as a solution in water); B) a single oral dose of L-DOPA (75 mg/kg, as a solution in water) administered by gavage; C) a single oral dose of (102) (267 mg/kg, as a solution in PEG400) administered by gavage. Animals were fasted overnight prior to the study and until 4 hours post-dosing. Serial blood samples were obtained

mixture was stirred for a total of 90 minutes. A solution containing an amino acid (5 mmol) in water (20 mL) containing saturated $NaHCO_3$ (25 mL) was added and the mixture stirred for an additional 2 h at room temperature. After removal of the THF *in vacuo*, saturated $NaHCO_3$ (15 mL) was added and the aqueous mixture washed with EtOAc (3 x 10 mL), then the pH adjusted to 3-4 with citric acid. The product was extracted into EtOAc (3 x 15 mL), and the combined organic phase dried over $MgSO_4$, and concentrated to dryness. The crude products (**105**) were used directly for coupling to L-Dopa as follows. The compounds were dissolved in anhydrous THF (60 mL) and triethylamine (0.70 mL, 5 mmol) added slowly with stirring. The solutions were cooled to -5°C in an ice-salt bath for 30 minutes, and ethyl chloroformate (0.24 mL, 2.4 mmol) added slowly, maintaining the temperature between 0 and 5°C. After addition was complete, the cold mixtures were stirred for a total of 90 minutes. A solution containing L-Dopa (5 mmol) in water (20 mL) containing saturated $NaHCO_3$ (25 mL) was added and the mixtures stirred for an additional 2 h at room temperature. After removal of the THF *in vacuo*, saturated $NaHCO_3$ (15 mL) was added and the aqueous mixtures washed with EtOAc (3 x 10 mL), then the pH adjusted to 3-4 with citric acid. The products were extracted into EtOAc (3 x 15 mL), and the combined organic phase dried over $MgSO_4$, and concentrated to dryness. The residues were purified by purified by preparative HPLC, using a Waters Nova-Pak C-18 column (19 x 300 mm) and eluting with a water/acetonitrile/0.05% formic acid gradient at 25 mL/min (30% MeCN ramping to 43% in 3 min, then to 53% MeCN by 22 min) to give the pure cholic acid L-Dopa dipeptide derivatives (**106**). Compounds were characterized by electrospray mass spectrometry as reported below:

Cholyl-Gly-L-Dopa (**106a**): MS (ESI) m/z 643.7($M-H^-$), 645.7 ($M+H^+$).

Cholyl-Val-L-Dopa (**106c**): MS (ESI) m/z 685.8 ($M-H^-$), 687.7 ($M+H^+$).

(107a): MS (ESI) m/z 614.4 ($M-H^-$), 616.3 ($M+H^+$).

(107b): MS (ESI) m/z 628.5 ($M-H^-$), 630.4 ($M+H^+$).

(107c): MS (ESI) m/z 676.4 ($M-H^-$), 678.3 ($M+H^+$).

(107d): MS (ESI) m/z 700.4 ($M-H^-$), 702.4 ($M+H^+$).

(107e): MS (ESI) m/z 644.4 ($M-H^-$), 646.3 ($M+H^+$).

(107f): MS (ESI) m/z 728.4 ($M-H^-$), 730.3 ($M+H^+$).

(107g): MS (ESI) m/z 657.5 ($M-H^-$), 659.4 ($M+H^+$).

The procedures set forth above for L-DOPA conjugated to a bile acid are also applicable to a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA. That is to say that by following the procedures set forth above and using the appropriate starting materials, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, or a derivatives of L-DOPA can be conjugated to such bile acids. It is understood, of course, that the use of appropriate protecting groups and reaction conditions to add and remove such groups may be necessary but such is well within the skill of the art.

In addition, the above procedures as well as the attached figures and supporting description thereof evidence that any drug containing a carboxyl group, an amine group and/or a hydroxyl group can be attached to bile acids to effect compounds having prolonged release *in vivo*.

Examples of drugs containing carboxyl groups include, for instance, angiotensin-converting enzyme inhibitors such as alecapril, captopril, 1-[4-carboxy-2-methyl-2R,4R-pentanoyl]-2,3-dihydro-2S-indole-2-carboxylic acid, enalaprilic acid, lisinopril, N-cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-2-methyl-1-oxopropyl]glycine, pivopril, quinaprilat, (2R,

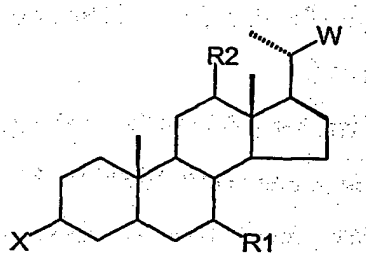
suprofen, tiaprofenic acid, tolfenamic acid, tolmetin and zopemirac; prostaglandins such as ciprostene, 16-deoxy-16-hydroxy-16-vinyl prostaglandin E_2, 6,16-dimethylprostaglandin E_2, epoprostostenol, meteneprost, nileprost, prostacyclin, prostaglandins E_1, E_2, or $F_{2\alpha}$ and thromboxane A_2; quinolone antibiotics such as acrosoxacin, cinoxacin, ciprofloxacin, enoxacin, flumequine, naladixic acid, norfloxacin, ofloxacin, oxolinic acid, pefloxacin, pipemidic acid and piromidic acid; other antibiotics such as aztreonam, imipenem, meropenem and related carbopenem antibiotics.

Representative drugs containing amine groups include: acebutalol, albuterol, alprenolol, atenolol, bunolol, bupropion, butopamine, butoxamine, carbuterol, cartelolol, colterol, deterenol, dexpropanolol, diacetolol, dobutamine, exaprolol, exprenolol, fenoterol, fenyripol, labotolol, levobunolol, metolol, metaproterenol, metoprolol, nadolol, pamatolol, penbutalol, pindolol, pirbuterol, practolol, prenalterol, primidolol, prizidilol, procaterol, propanolol, quinterenol, rimiterol, ritodrine, solotol, soterenol, sulfiniolol, sulfinterol, sulictidil, tazaolol, terbutaline, timolol, tiprenolol, tipridil, tolamolol, thiabendazole, albendazole, albutoin, alendronate, alinidine, alizapride, amiloride, aminorex, aprinocid, cambendazole, cimetidine, cisapride, clonidine, cyclobenzadole, delavirdine, efegatrin, etintidine, fenbendazole, fenmetazole, flubendazole, fludorex, icadronate, lobendazole, mebendazole, metazoline, metoclopramide, methylphenidate, mexiletine, neridronate, nocodazole, oxfendazole, oxibendazole, oxmetidine, pamidronate, parbendazole, pramipexole, prazosin, procainamide, ranitidine, tetrahydrazoline, tiamenidine, tinazoline, tiotidine, tocainide, tolazoline, tramazoline, xylometazoline, dimethoxyphenethylamine, N-[3(R)-[2-piperidin-4-yl)ethyl]-2-piperidone-1-yl]acetyl-3(R)-methyl-β-alanine, adrenolone, aletamine, amidephrine, amphetamine, aspartame, bamethan, betahistine, clorprenaline, chlortermine, dopamine, ephrinephrine

olpadronate, residronate, YH-529 and zolendronate; protease inhibitors such as ciprokiren, enalkiren, ritonavir, saquinavir and terlakiren; prostaglandins such as arbaprostil, carboprost, misoprostil and prostacydin; antidepressives such as 8-hydroxychlorimipramine and 2-hydroxyimipramine; antihypertonics such as sotarol and fenoldopam; anticholinerogenics such as biperidine, procyclidin and trihexyphenidal; antiallergenics such as cromolyn; glucocorticoids such as betamethasone, budenosid, chlorprednison, clobetasol, clobetasone, corticosteron, cortisone, cortodexon, dexamethason, flucortolon, fludrocortisone, flumethasone,flunisolid, fluprednisolon, flurandrenolide, flurandrenolon acetonide, hydrocortisone, meprednisone, methylpresnisolon, paramethasone, prednisolon, prednisol, triamcinolon and triamcinolon acetonide; narcotic agonists and antagonists such as apomorphine, buprenorphine, butorphanol, codein, cyclazocin, hydromorphon, ketobemidon, levallorphan, levorphanol, metazocin, morphine, nalbuphin, nalmefen, naloxon, nalorphine, naltrexon, oxycodon, oxymorphon and pentazocin; stimulants such asmazindol and pseudoephidrine; anaesthetics such as hydroxydion and propofol; β-receptor blockers such as acebutolol, albuterol, alprenolol, atenolol, betazolol, bucindolol, cartelolol, celiprolol, cetamolol, labetalol, levobunelol, metoprolol, metipranolol, nadolol, oxyprenolol, pindolol, propanolol and timolol; α-sympathomimetics such as adrenalin, metaraminol, midodrin, norfenefrin, octapamine, oxedrin, oxilofrin, oximetazolin and phenylefrin; β-sympathomimetics such as bamethan, clenbuterol, fenoterol, hexoprenalin, isoprenalin, isoxsuprin, orciprenalin, reproterol, salbutamol and terbutalin; bronchodilators such as carbuterol, dyphillin, etophyllin, fenoterol, pirbuterol, rimiterol and terbutalin; cardiotonics such as digitoxin, dobutamin, etilefrin and prenalterol; antimycotics such as amphotericin B, chlorphenesin, nystatin and perimycin; anticoagulants such as acenocoumarol, dicoumarol,

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein:

R^1 is selected from the group consisting of hydrogen and OH;

R^2 is selected from the group consisting of hydrogen and OH;

X is selected from the group consisting of OH and D-Y-, where Y is selected from the group consisting of a covalent bond and a cleavable linker group covalently connecting D to the steroid;

D is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

W is selected from the group consisting of (a) a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group consisting of –COOH, $-SO_3H$, $-SO_2H$, $-P(O)(OR^6)(OH)$, $-OP(O)(OR^6)(OH)$, $-OSO_3H$ and pharmaceutically acceptable salts thereof, where R^6 is selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl; and (b) a group of the formula:

–M–Y'–D'

D' is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

Q is CH_2 or O;

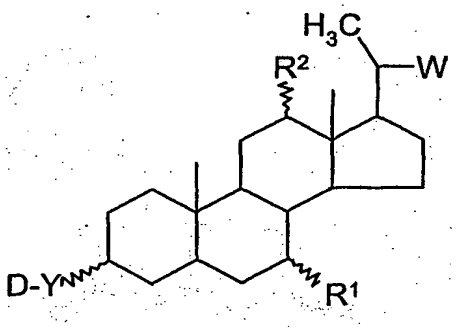
R^1 is selected from the group consisting of H and OH;

R^2 is selected from the group consisting of H and OH;

wherein the compound of formula (I-a) above is a substrate for an intestinal bile acid transporter;

or pharmaceutically acceptable salts thereof.

3. A compound of the formula (I-b):



(I-b)

wherein:

Y is selected from the group consisting of a covalent bond and a cleavable linker group covalently connecting D to the steroid;

D is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

R^1 is selected from the group consisting of H and OH;

R^2 is selected from the group consisting of H and OH;

W is a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group

D is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

Q is CH_2 or O;

R^1 is selected from the group consisting of H and OH;

R^2 is selected from the group consisting of H and OH;

wherein the compound of formula (I-c) above is a substrate for an intestinal bile acid transporter;

or pharmaceutically acceptable salts thereof.

5. The compound according to Claim 1, wherein W is selected from the group consisting of $-CH_2CH_2CO_2H$, $-CH_2CH_2CONHCH_2CO_2H$, $-CH_2CH_2CONHCH_2CH_2SO_3H$, and pharmaceutically acceptable salts thereof.

6. The compound according to Claim 1, wherein W is selected from the group of the formula:

$$-M-Y'-D'$$

wherein:

M is selected from the group consisting of $-CH_2OC(O)-$ and $-CH_2CH_2C(O)-$;

Y' is a covalent bond or a cleavable linker group covalently connecting D' to M;

D' is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 1 wherein D and/or D′ is L-DOPA or a derivative of L-DOPA, or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 1, wherein X is –Y-D and D is L-DOPA, a derivative of L-DOPA, or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 11, wherein W is –M–Y′-D′, or a pharmaceutically acceptable salt thereof.

13. The compound according to Claim 12, wherein D′ is L-DOPA, a derivative of L-DOPA, or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 12, wherein D′ is a catechol O-methyl transferase inhibitor or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 12, wherein D′ is a L-aromatic amino acid decarboxylase inhibitor or a pharmaceutically acceptable salt thereof.

16. The compound according to Claim 1, wherein X is –Y-D, or a pharmaceutically acceptable salt thereof.

-C(O)OCR^{11}R^{12}OC(O)NR^{7}-, with the underlined atom being derived from a hydroxyl, NH, carboxylic acid moiety of the drug D or D';

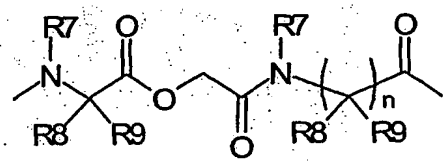
each R^{7} is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

R^{11} and R^{12} are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{11} and R^{12} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring;

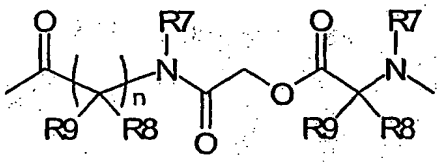
Z is selected from the group consisting of a bond, –O-, -S-, -C(O)O-, -OC(O)O-, -NR^{7}C(O)O-, -OC(O)NR^{7}-, -OP(O)(OR^{6})O-, -P(O)(OR^{6})O-, - NR^{7}P(O)(OR^{6})O-, -C(O)NR^{7}-, -NR^{7}C(O)NR^{7}-, -NR^{7}C(O)NR^{7}-, -S(O)$_2$NR^{7}-, -S(O)-, -S(O)$_2$-, -C(O)S-, -ON=, -C(O)ON=, -NR^{7}C(O)ON=, -C(O)OCR^{11}R^{12}ON=, and a C=C linkage, wherein R^{6}, R^{7}, R^{11}, and R^{12} are defined as above;

Y* is a bond or a bivalent hydrocarbyl radical of 1 to 18 atoms having at least one alkylene, alkenylene or alkynylene group, with said at least one alkylene, alkenylene or alkynylene group optionally replaced with –O-, -S-, -NR^{7}-, -C(O)-, -C(S)-, -OC(O)-, -C(O)O-, -SC(O)-, -C(O)S-, -SC(S)-, -C(S)S-, -C(O)NR^{7}-, -NR^{7}C(O)-, arylene, substituted arylene, cycloalkylene, substituted cycloalkylene, cycloalkenylene, substituted cycloalkenylene, bivalent heterocyclic group or substituted bivalent heterocyclic group.

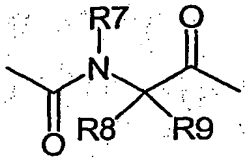
22. The compound according to Claim 21, wherein said bivalent hydrocarbyl radical, Y*, is 1 to 10 atoms in length.



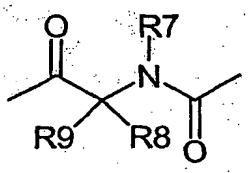
(xiv)



(xv)



(xvi)



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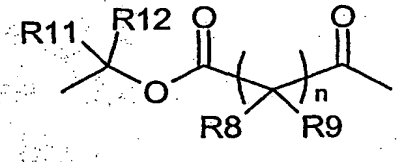

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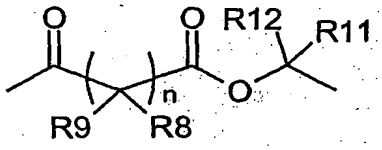

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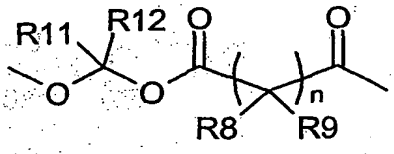

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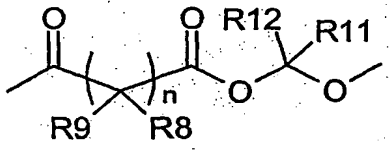
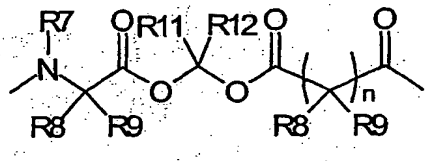
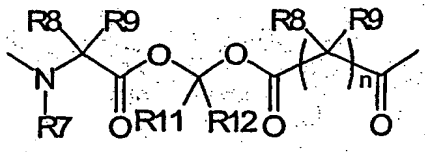


(xxi)



(xxii)



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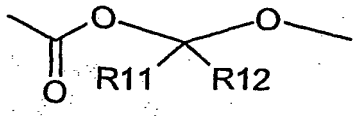
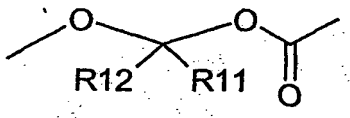
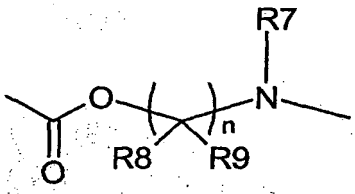


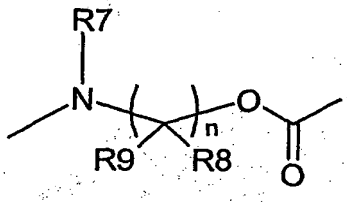
(xxxiv)



(xxxv)



(xxxvi)



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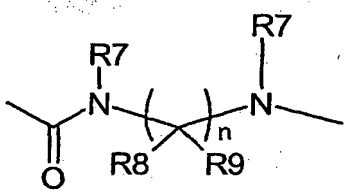

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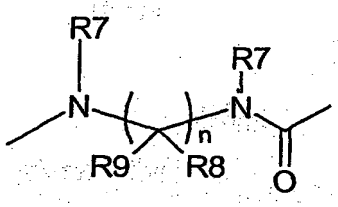
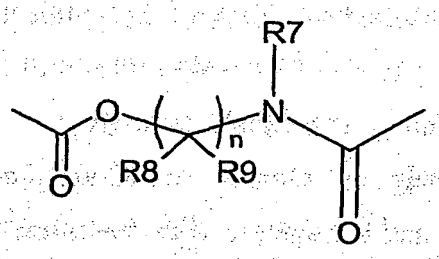
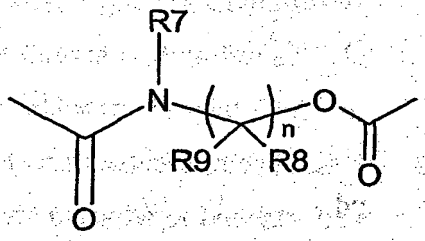


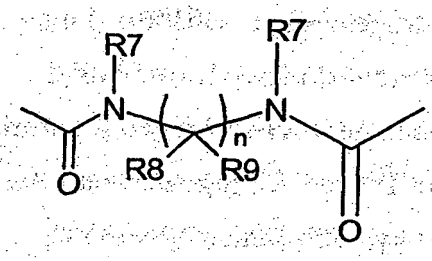
(xxxix)



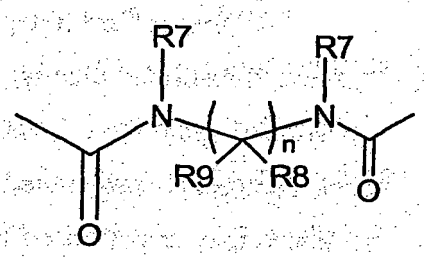
(xl)



(xli)



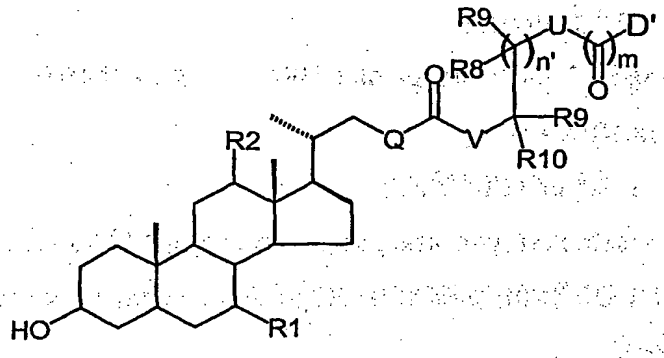
(xlii)



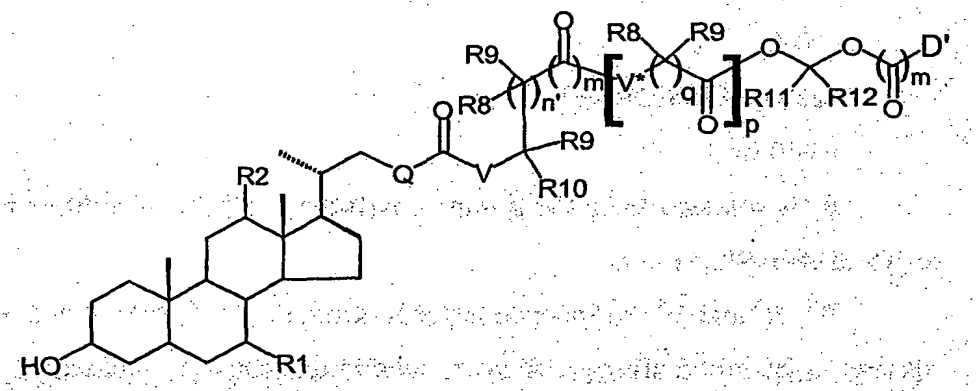
(xliii)

or pharmaceutically acceptable salts thereof.

25. The compound according to Claim 2 having formulae (I-a-1) or (I-a-2):



(I-a-1)



(I-a-2)

wherein:

D' is a member selected from the group consisting of L-DOPA, a catechol O-methyl transferase inhibitor, an inhibitor of a L-aromatic amino acid decarboxylase, and derivatives of L-DOPA;

Q is CH_2 or O;

R^1 and R^2 are one of the following combinations:

R^{11} and R^{12} are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{11} and R^{12} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycle or substituted heterocyclic ring;

or pharmaceutically acceptable salts thereof.

26. A compound of claim 2 having formula (I-a) wherein;

Q is CH_2;

R^1 and R^2 are α-OH;

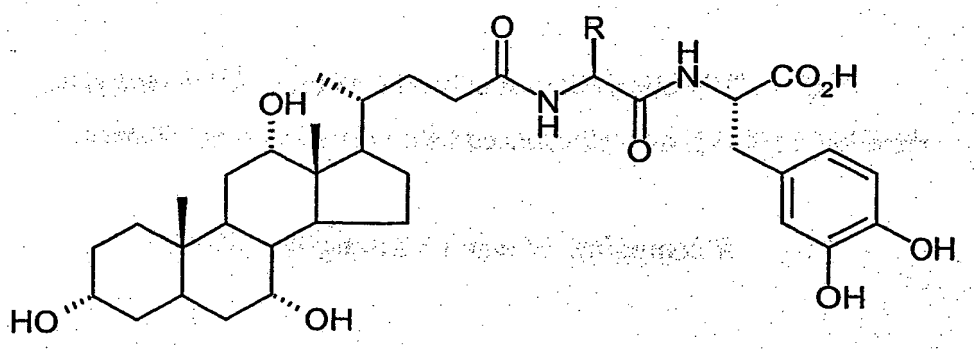
Y' is derived from an α-amino acid; and

D' is a derivative of L-DOPA.

or a pharmaceutically acceptable salt thereof.

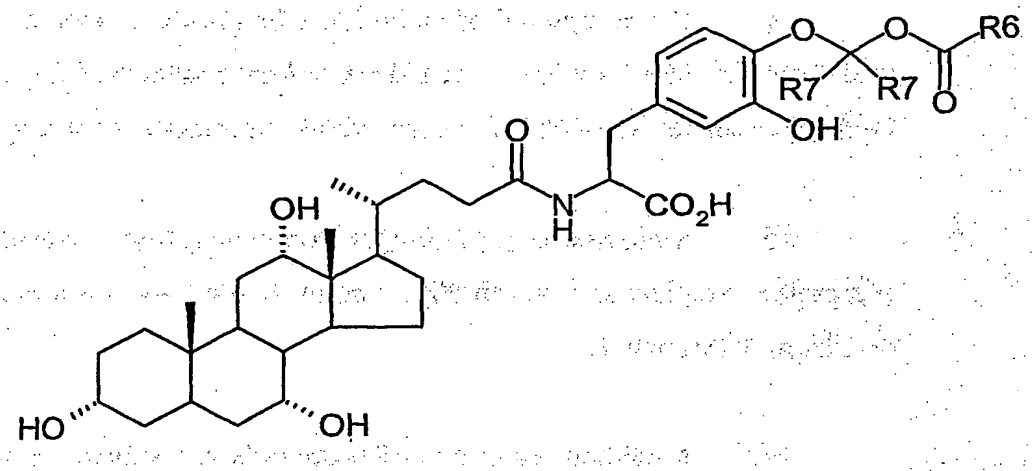
27. The compound of claim 26, wherein Y' is derived from one of the 20 genetically encoded amino acids.

28. The compound of claim 27 having formula (xlix):



(xlix)

wherein:



(Ii)

wherein:

R^6 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl and substituted heteroaryl; and

each R^7 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl and substituted heteroaryl;

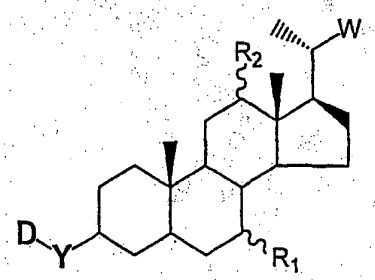
or a pharmaceutically acceptable salt thereof.

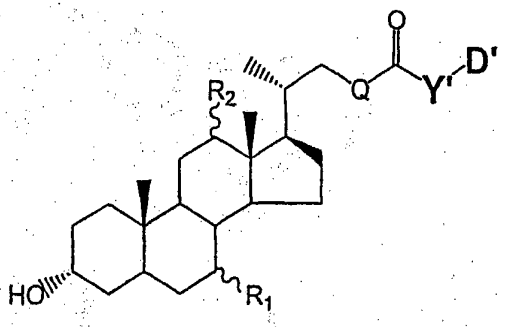
32. The compound of claim 31 wherein R^6 is selected from the group consisting of lower alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl and R^7 is selected from the group consisting of hydrogen and lower alkyl.

33. The compound of claim 32 wherein R^6 is selected from the group consisting of methyl and *tert*-butyl and R^7 is selected from the group consisting of hydrogen and methyl.

Figure 1

Bile Acid Prodrug Derivatives for Sustained Release of L-Dopa and Inhibitors of L-Dopa Metabolism



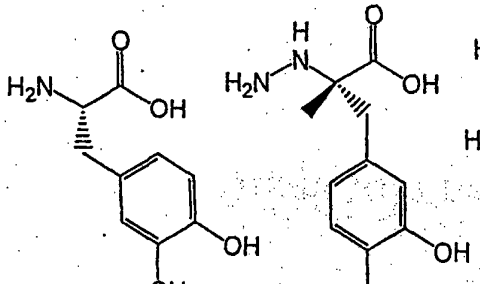


Y, Y' are (optionally) linker groups

D, D' are selected from L-Dopa, Carbidopa, Benserazide, Entacapone, Tolcapone or Nitecapone

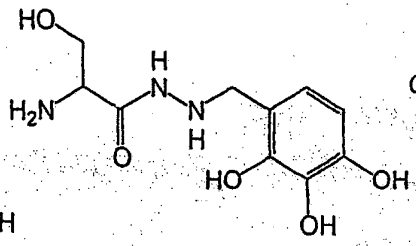
R1 and R2 = H or OH

W is (a) a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group consisting of -COOH, $-SO_3H$, $-SO_2H$, -P(O)(OR6)(OH), -OP(O)(OR6)(OH), $-OSO_3H$ and the like and pharmaceutically acceptable salts thereof, where R6 is selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl; and (b) a group of formula $CH_2QC(O)$-Y'-D'

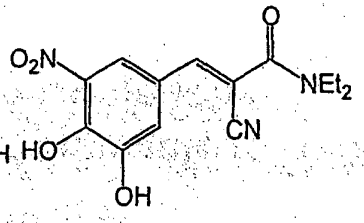


L-Dopa

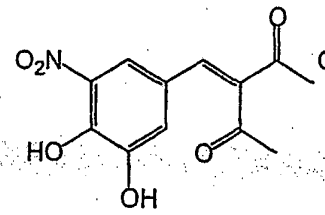
Carbidopa



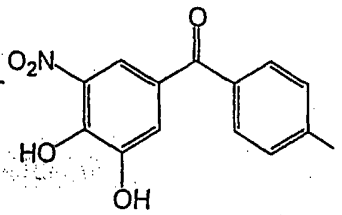
Benserazide



Entacapone



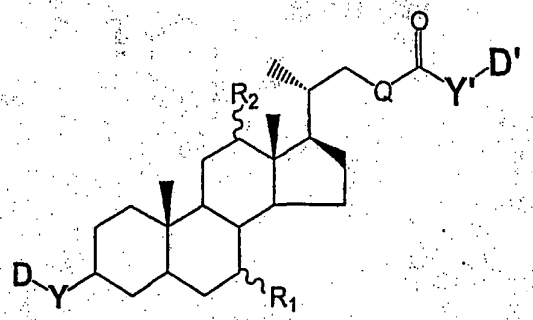
Nitecapone



Tolcapone

Figure 3:

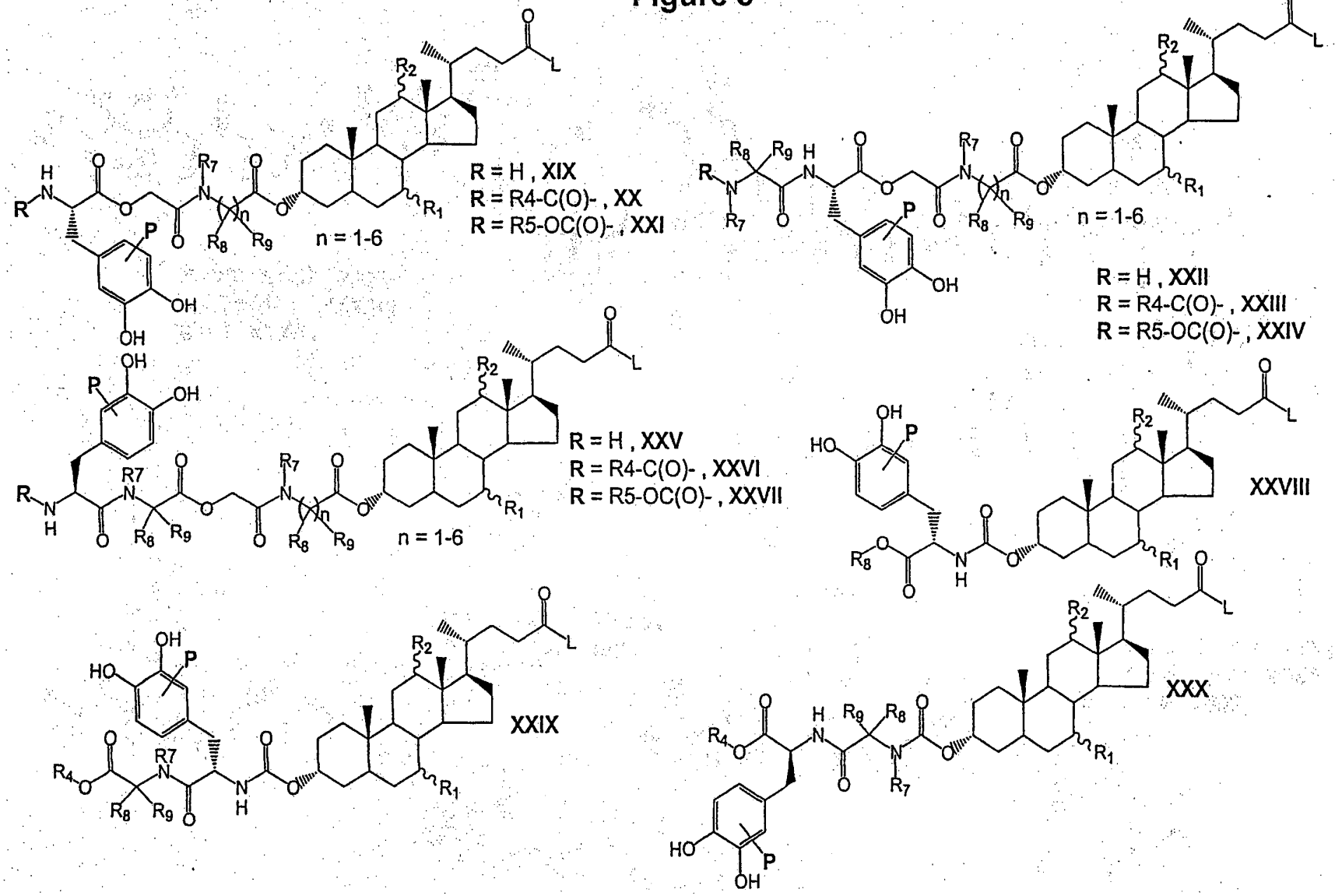
Multi Drug - Bile Acid Derivatives for Sustained Release of L-Dopa



a: R1 = R2 = α-OH; **b:** R1 = α-OH, R2 = H; **c:** R1 = β-OH, R2 = H; **d:** R1 = H, R2 = α-OH; **e:** R1 = β-OH, R2 = α-OH; **f:** R1 = R2 = H

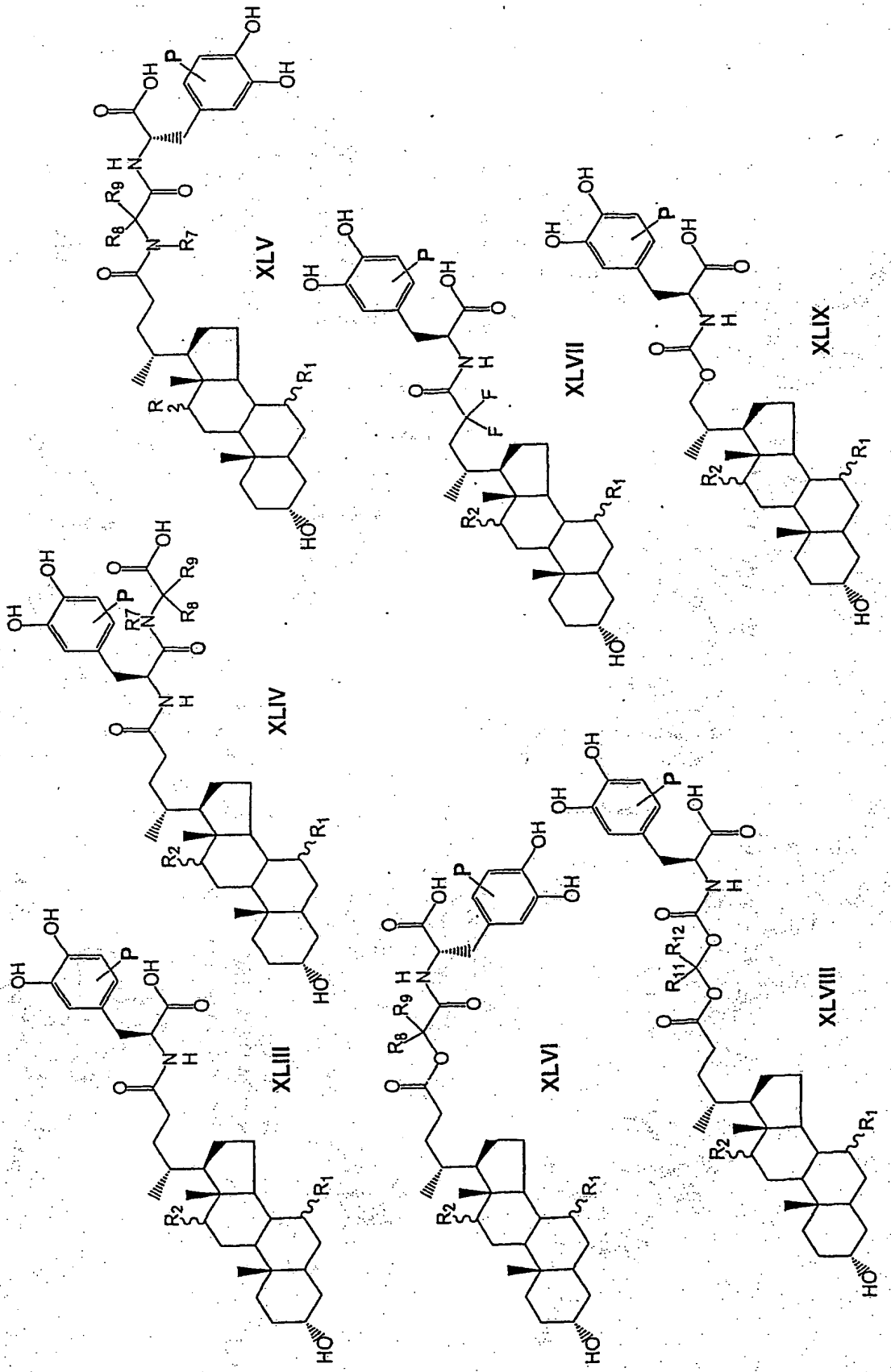
Y, Y' are (optionally) linker groups
D, D' are selected from L-Dopa, Carbidopa, Benserazide, Entacapone, Tolcapone or Nitecapone such that at least one of D and D' is L-Dopa
Q is CH_2 or O

Figure 5



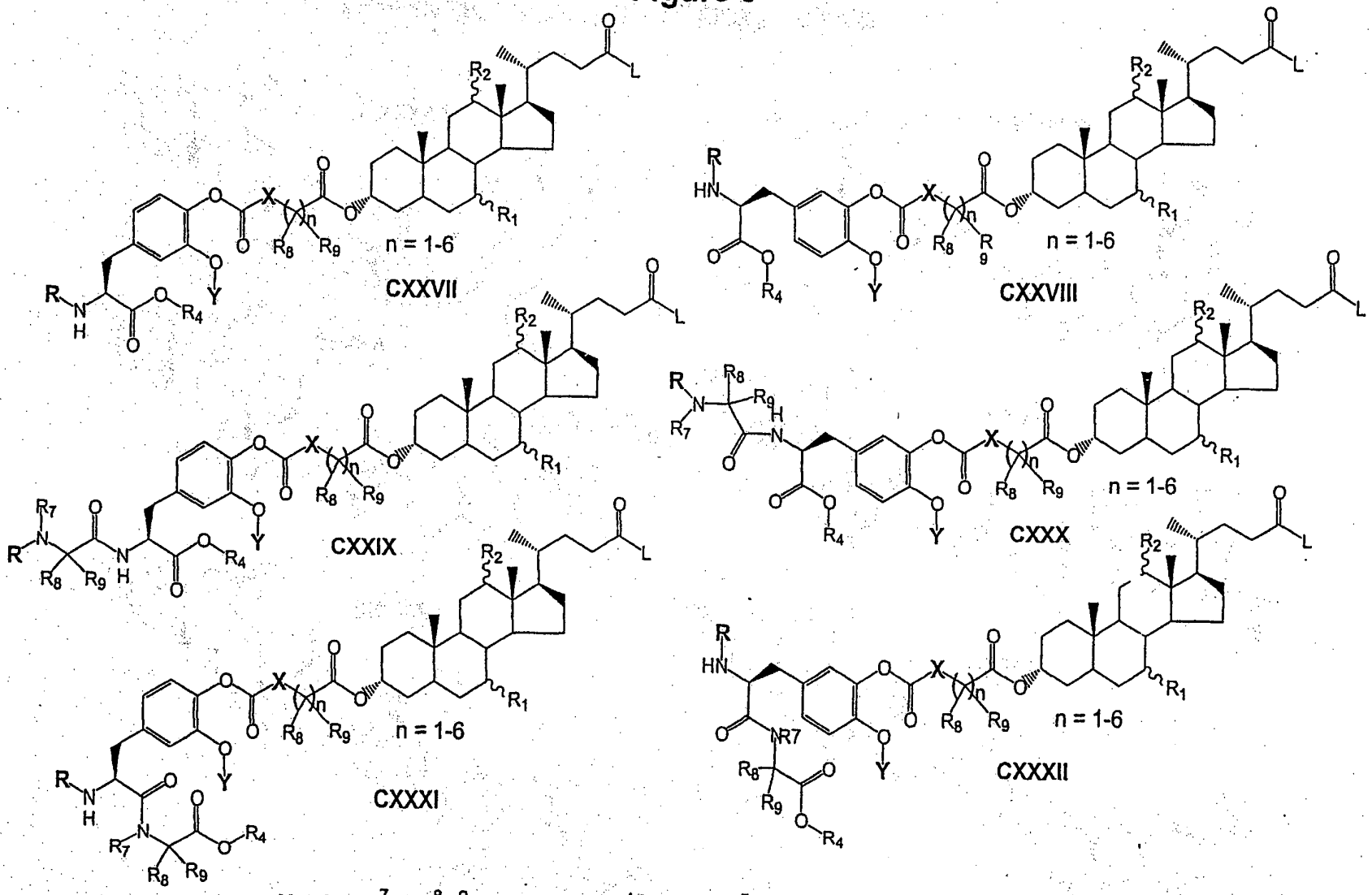
a: R1 = R2 = α-OH; b: R1 = α-OH, R2 = H; c: R1 = β-OH, R2 = H; d: R1 = H, R2 = α-OH; e: R1 = β-OH, R2 = α-OH; f: R1 = R2 = H
L = hydroxy or an alkylamino group substituted with a substituent selected from the group consisting of
CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

Figure 7



a: R1 = R2 = α-OH; b: R1 = α-OH, R2 = H; c: R1 = β-OH, R2 = H; d: R1 = H, R2 = α-OH; e: R1 = β-OH, R2 = α-OH; f: R1 = R2 = H

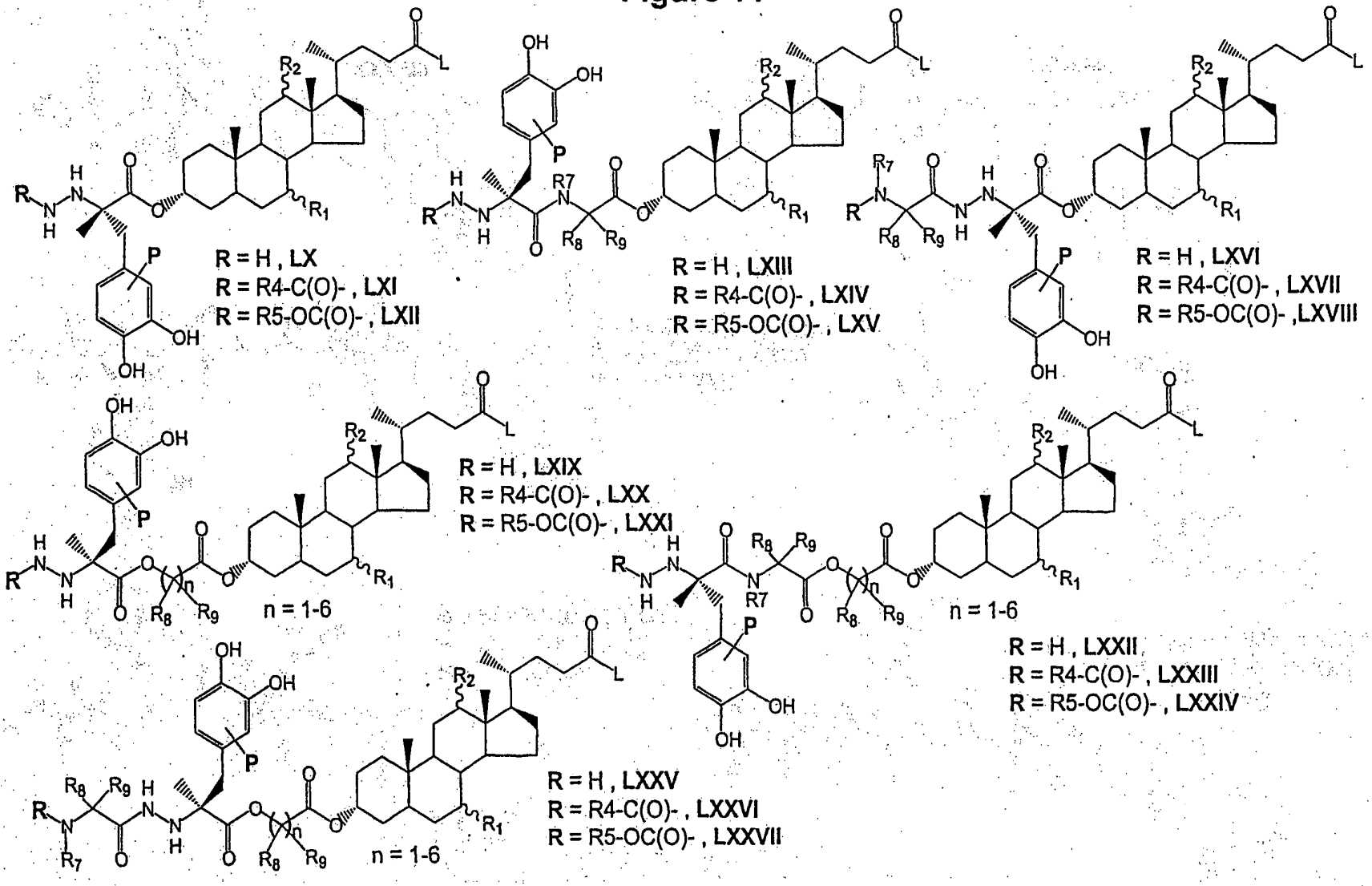
Figure 9



X = O, NR^7, CR^8R^9 ; Y = H, $-C(O)R^4$, $-C(O)OR^5$; R = H, $-C(O)R^4$, $-C(O)OR^5$

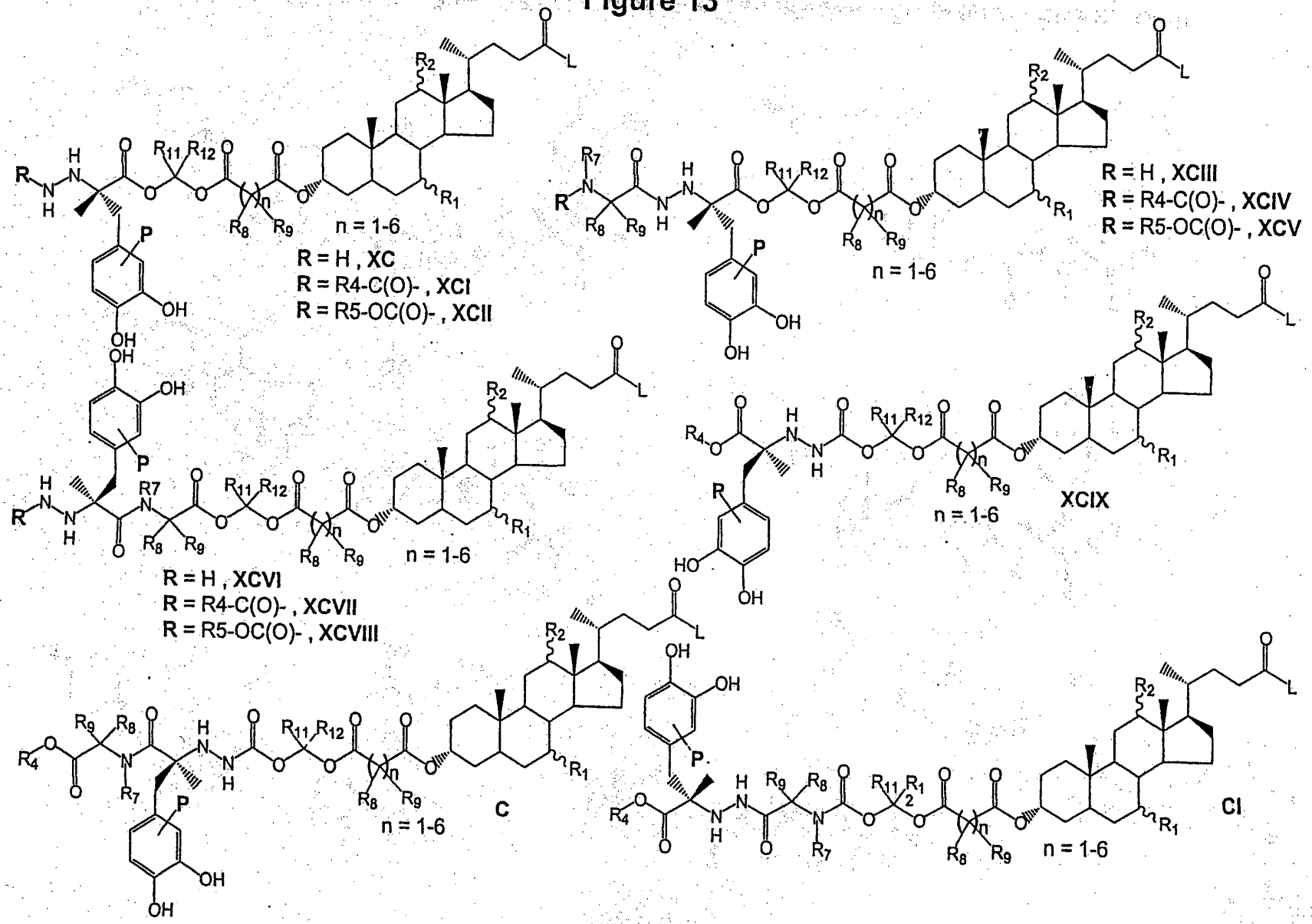
a: R1 = R2 = α-OH; **b:** R1 = α-OH, R2 = H; **c:** R1 = β-OH, R2 = H; **d:** R1 = H, R2 = α-OH; **e:** R1 = β-OH, R2 = α-OH; **f:** R1 = R2 = H
L = hydroxy or an alkylamino group substituted with a substituent selected from the group consisting of
CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

Figure 11



a: R1 = R2 = α-OH; b: R1 = α-OH, R2 = H; c: R1 = β-OH, R2 = H; d: R1 = H, R2 = α-OH; e: R1 = β-OH, R2 = α-OH; f: R1 = R2 = H
L = hydroxy or an alkylamino group substituted with a substituent selected from the group consisting of
CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

Figure 13

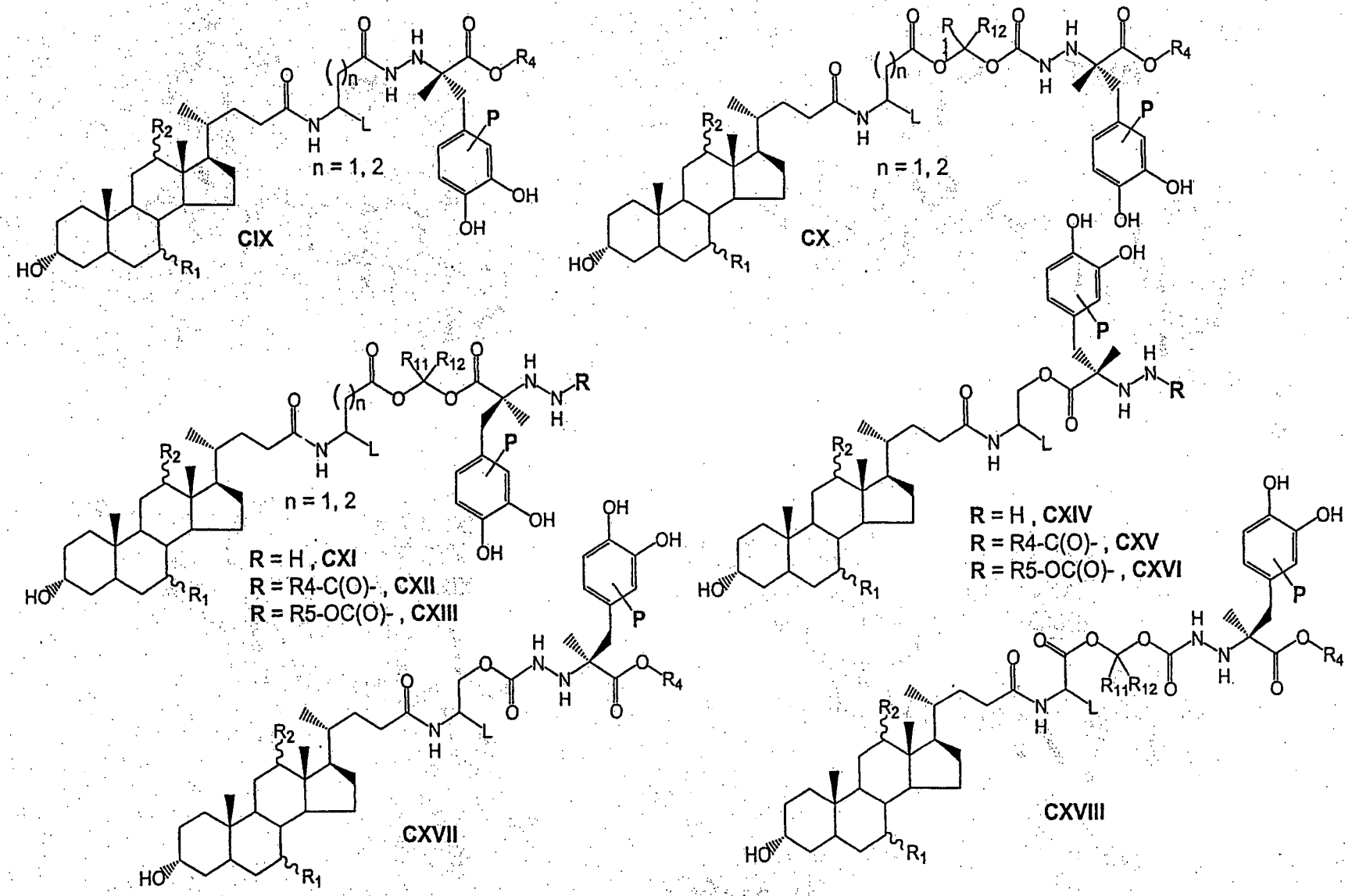


a: R1 = R2 = α-OH; b: R1 = α-OH, R2 = H; c: R1 = β-OH, R2 = H; d: R1 = H, R2 = α-OH; e: R1 = β-OH, R2 = α-OH; f: R1 = R2 = H

L = hydroxy or an alkylamino group substituted with a substituent selected from the group consisting of

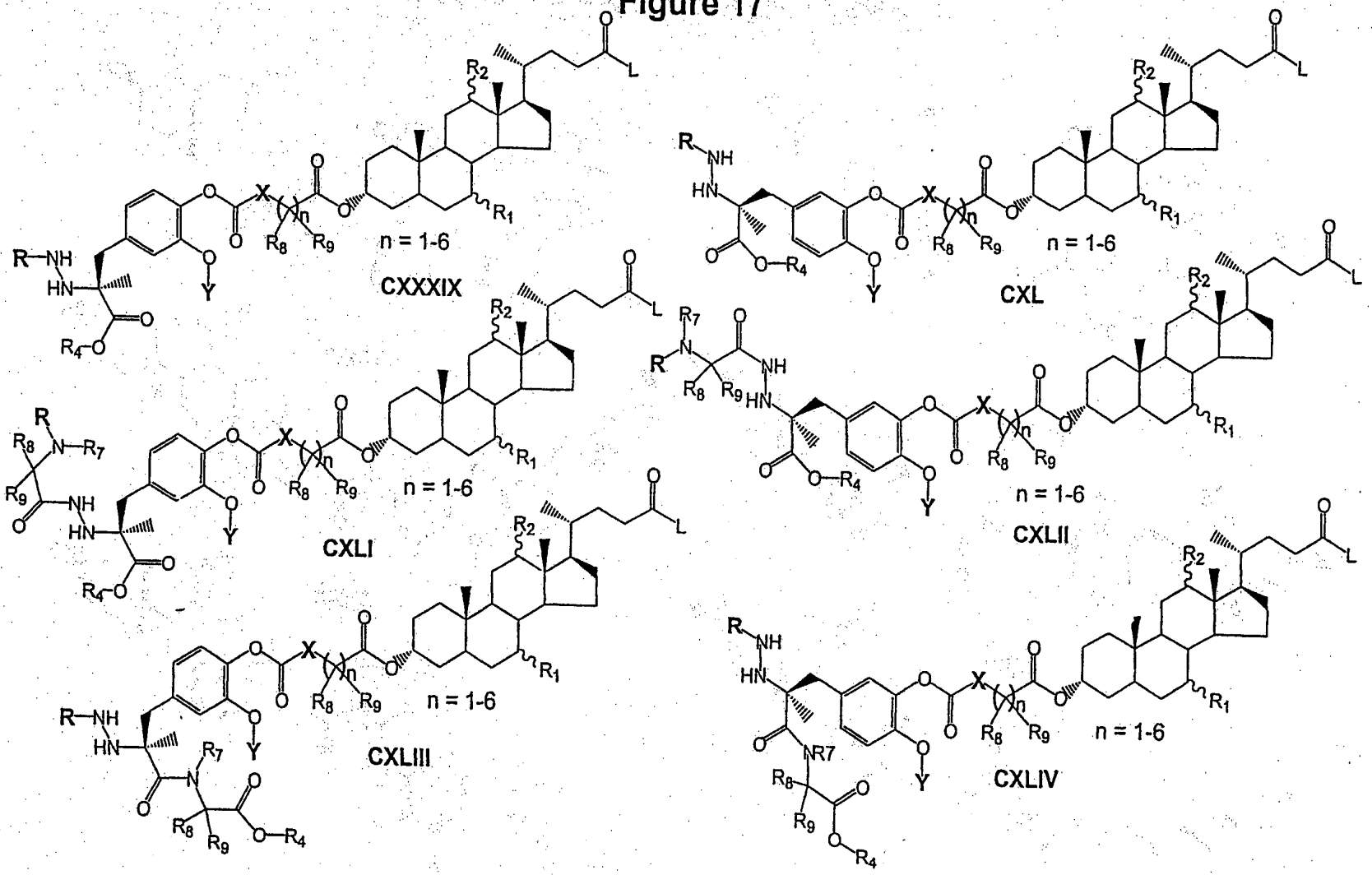
CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

Figure 15



a: R1 = R2 = α-OH; b: R1 = α-OH, R2 = H; c: R1 = β-OH, R2 = H; d: R1 = H, R2 = α-OH; e: R1 = β-OH, R2 = α-OH; f: R1 = R2 = H
L = CO_2H or an alkylamino group substituted with a substituent selected from the group consisting of
CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

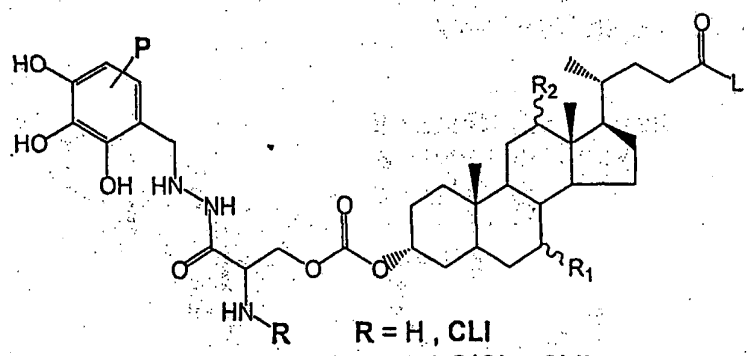
Figure 17



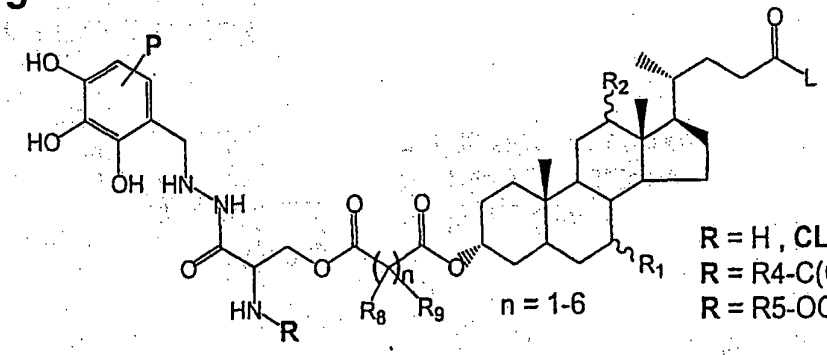
X = O, NR^7, CR^8R^9 ; Y = H, $-C(O)R^4$, $-C(O)OR^5$; R = H, $-C(O)R^4$, $-C(O)OR^5$

a: R1 = R2 = α-OH; **b:** R1 = α-OH, R2 = H; **c:** R1 = β-OH, R2 = H; **d:** R1 = H, R2 = α-OH; **e:** R1 = β-OH, R2 = α-OH; **f:** R1 = R2 = H
L = hydroxy or an alkylamino group substituted with a substituent selected from the group consisting of
CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

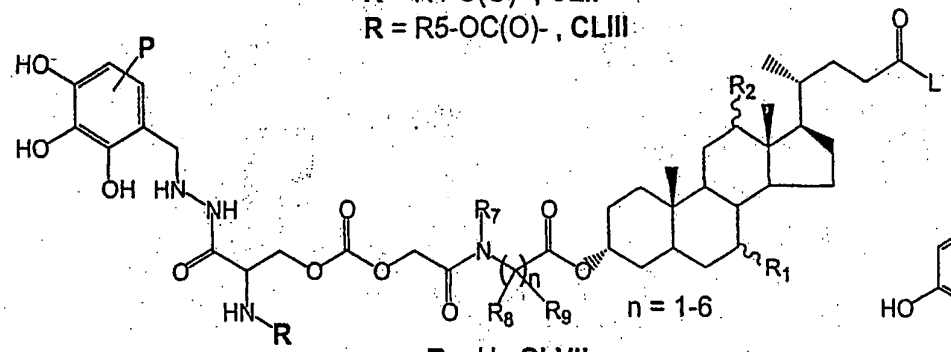
Figure 19



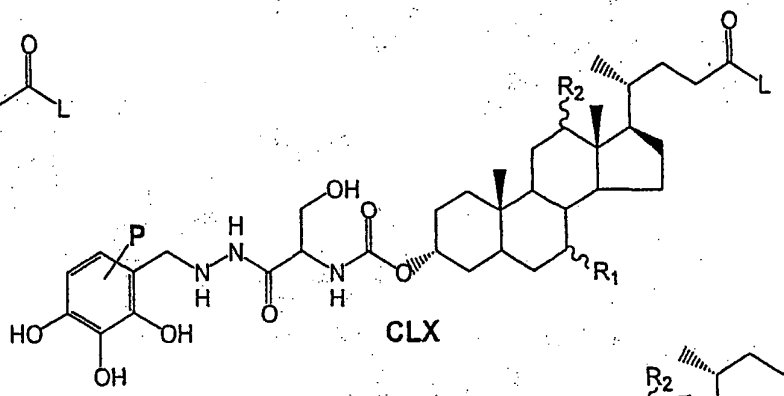
R = H , CLI
R = R4-C(O)- , CLII
R = R5-OC(O)- , CLIII



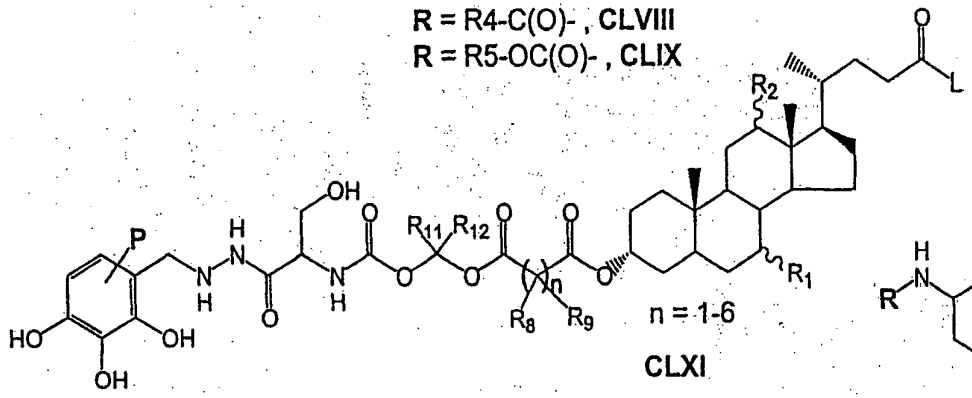
R = H , CLIV
R = R4-C(O)- , CLV
R = R5-OC(O)- , CLVI



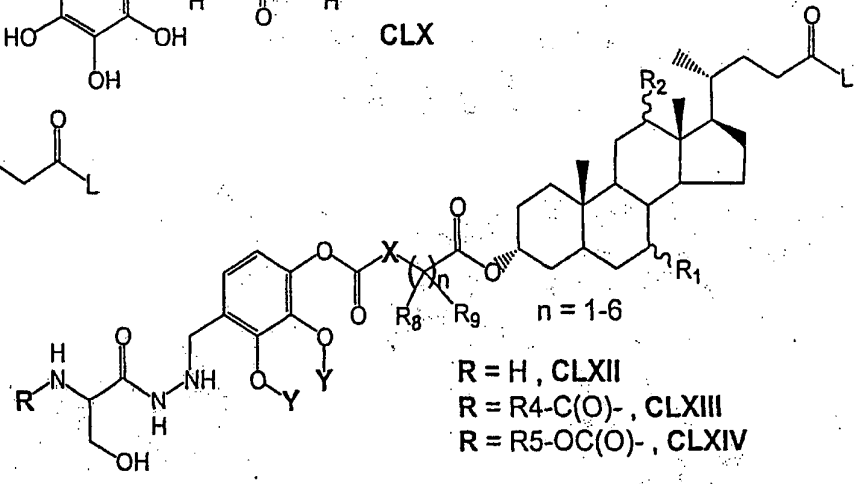
R = H , CLVII
R = R4-C(O)- , CLVIII
R = R5-OC(O)- , CLIX



CLX



CLXI

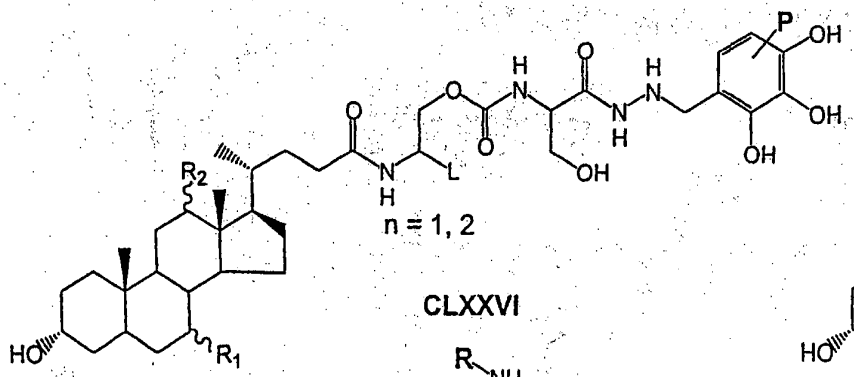


R = H , CLXII
R = R4-C(O)- , CLXIII
R = R5-OC(O)- , CLXIV

X = O, NR^7, CR^8R^9 ; Y = H, $-C(O)R^4$, $-C(O)OR^5$; R = H, $-C(O)R^4$, $-C(O)OR^5$

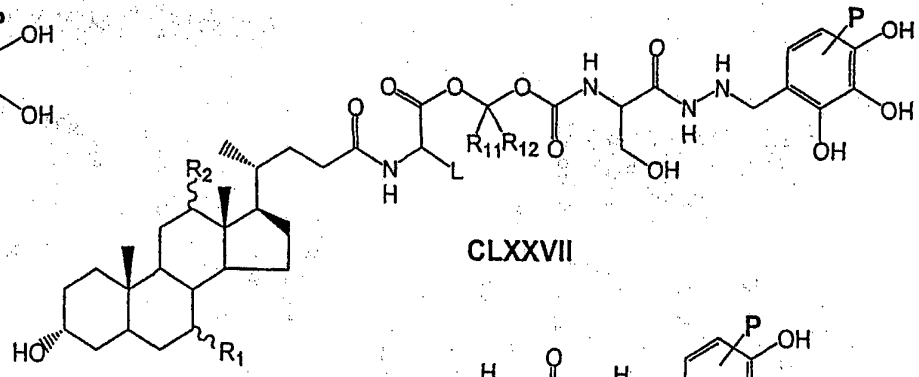
a: R1 = R2 = α-OH; b: R1 = α-OH, R2 = H; c: R1 = β-OH, R2 = H; d: R1 = H, R2 = α-OH; e: R1 = β-OH, R2 = α-OH; f: R1 = R2 = H
L = hydroxy or an alkylamino group substituted with a substituent selected from the group consisting of
CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

Figure 21

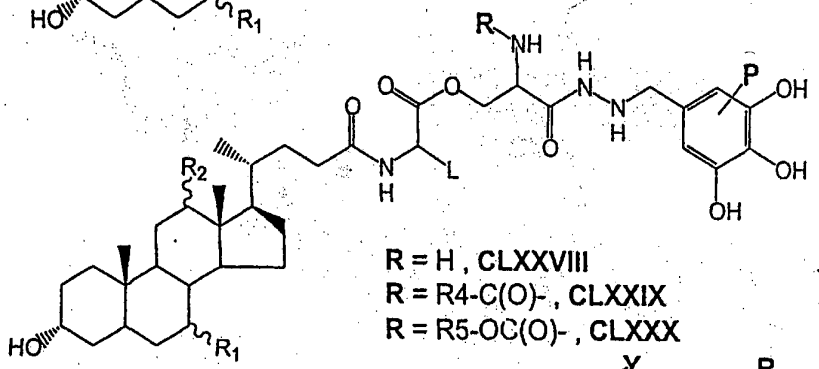


n = 1, 2

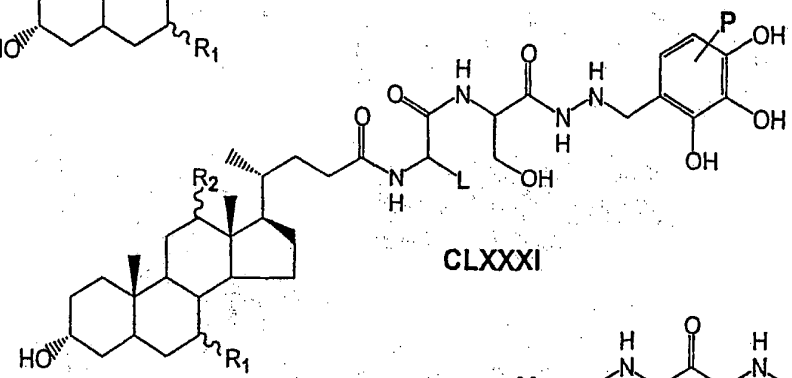
CLXXVI



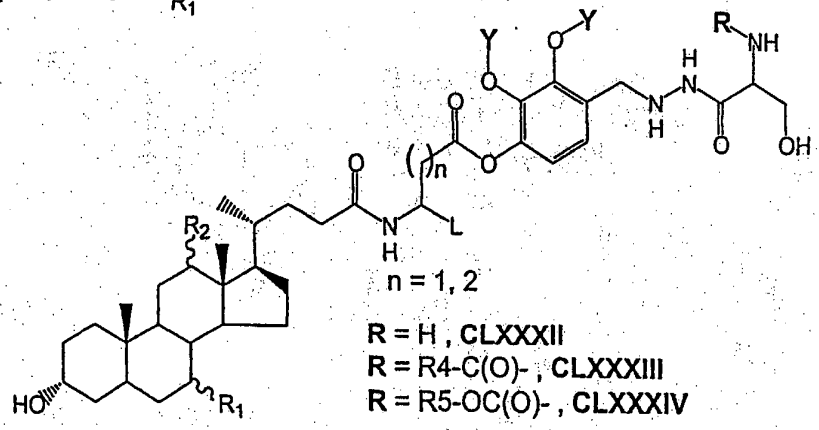
CLXXVII



R = H , CLXXVIII
R = R4-C(O)- , CLXXIX
R = R5-OC(O)- , CLXXX

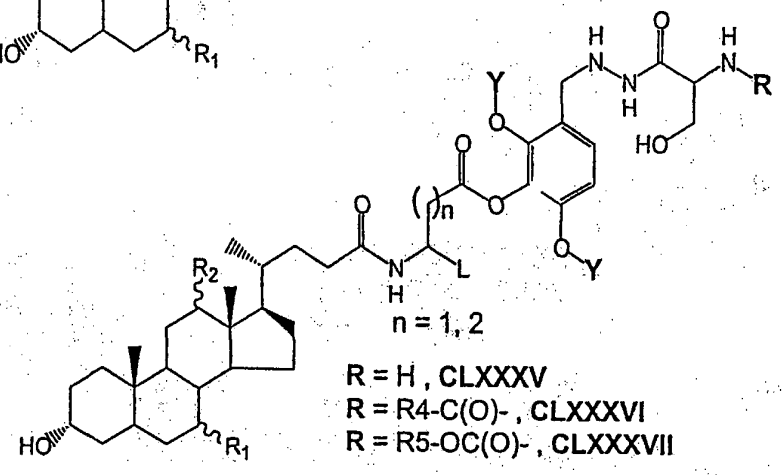


CLXXXI



n = 1, 2

R = H , CLXXXII
R = R4-C(O)- , CLXXXIII
R = R5-OC(O)- , CLXXXIV



n = 1, 2

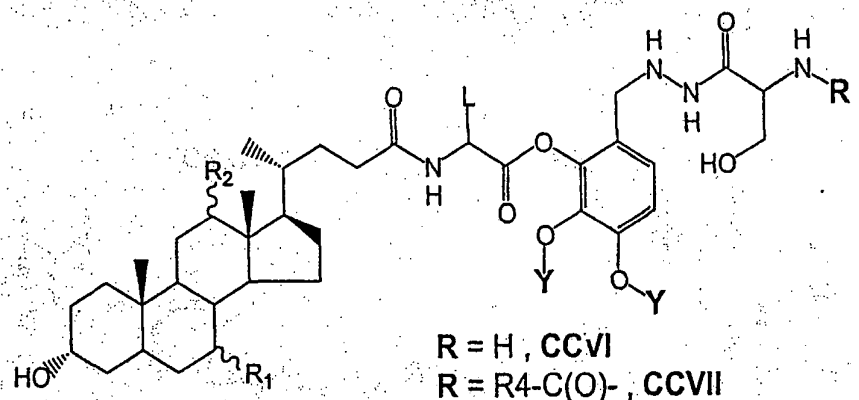
R = H , CLXXXV
R = R4-C(O)- , CLXXXVI
R = R5-OC(O)- , CLXXXVII

X = O, NR^7, CR^8R^9 ; Y = H, $-C(O)R^4$, $-C(O)OR^5$

a: R1 = R2 = α-OH; b: R1 = α-OH, R2 = H; c: R1 = β-OH, R2 = H; d: R1 = H, R2 = α-OH; e: R1 = β-OH, R2 = α-OH; f: R1 = R2 = H

L = CO_2H or an alkylamino group substituted with a substituent selected from the group consisting of CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

Figure 23



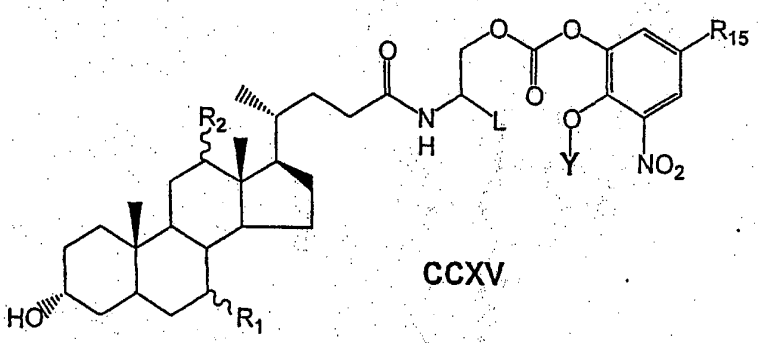
R = H , **CCVI**
R = R4-C(O)- , **CCVII**
R = R5-OC(O)- , **CCVIII**

Y = H, $-C(O)R^4$, $-C(O)OR^5$

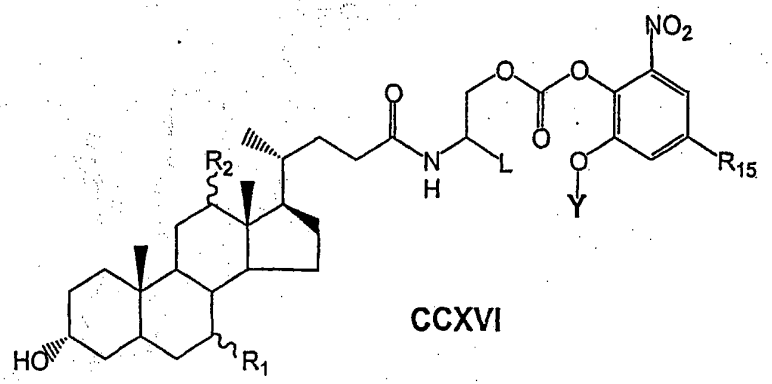
a: R1 = R2 = α-OH; **b:** R1 = α-OH, R2 = H; **c:** R1 = β-OH, R2 = H; **d:** R1 = H, R2 = α-OH; **e:** R1 = β-OH, R2 = α-OH; **f:** R1 = R2 = H

L = CO_2H or an alkylamino group substituted with a substituent selected from the group consisting of
CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

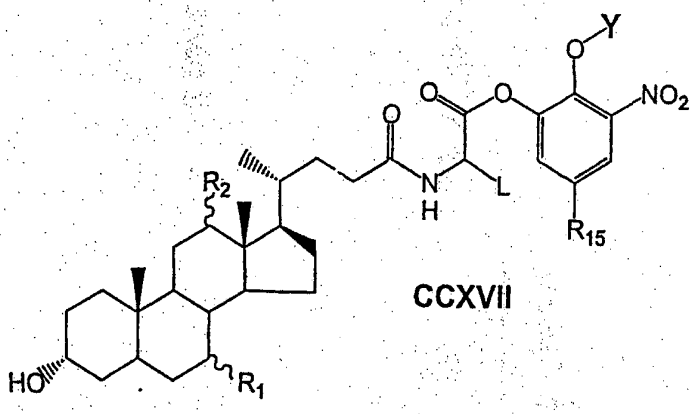
Figure 25



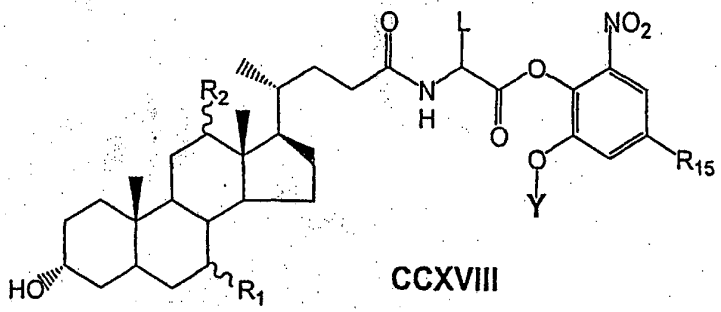
CCXV



CCXVI

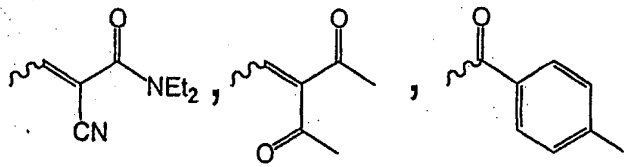


CCXVII



CCXVIII

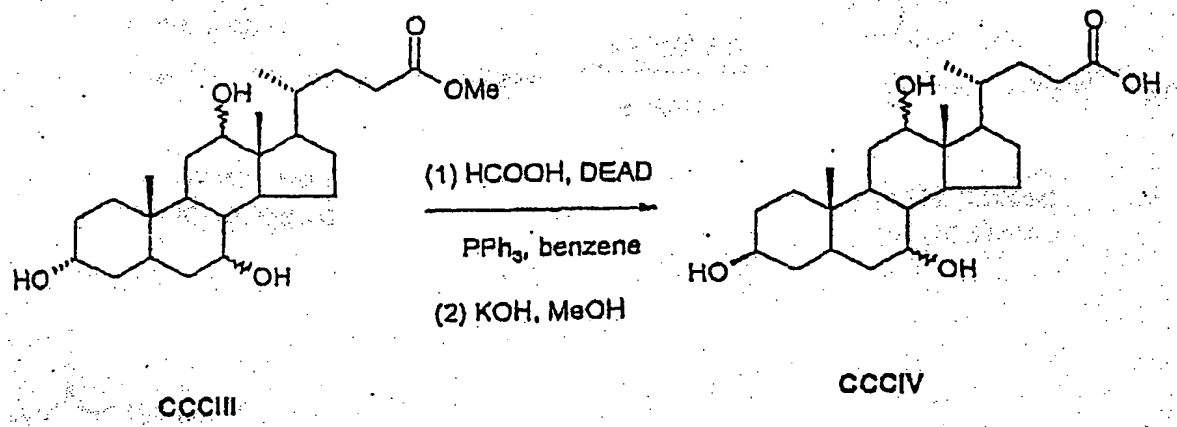
Y = H, $-C(O)R^4$, $-C(O)OR^5$

R15 = 

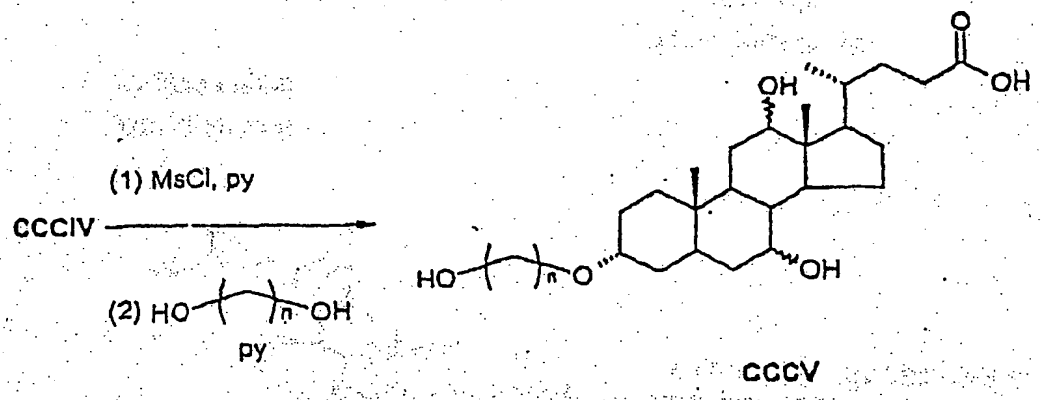
a: R1 = R2 = α-OH; **b:** R1 = α-OH, R2 = H; **c:** R1 = β-OH, R2 = H; **d:** R1 = H, R2 = α-OH; **e:** R1 = β-OH, R2 = α-OH; **f:** R1 = R2 = H

L = OH, CO_2H or an alkylamino group substituted with a substituent selected from the group consisting of CO_2H, SO_3H, SO_2H, $P(O)(OR^6)OH$, $OP(O)(OR^6)OH$, OSO_3H; or a pharmaceutically acceptable salt thereof

FIGURE 27



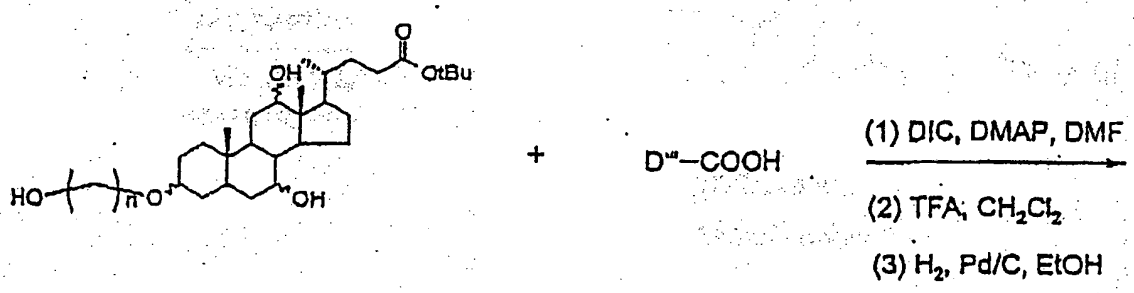
CCCIII CCCIV



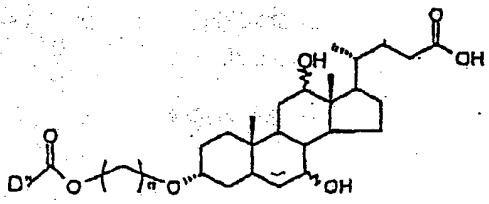
CCCV

Scheme 2

FIGURE 29

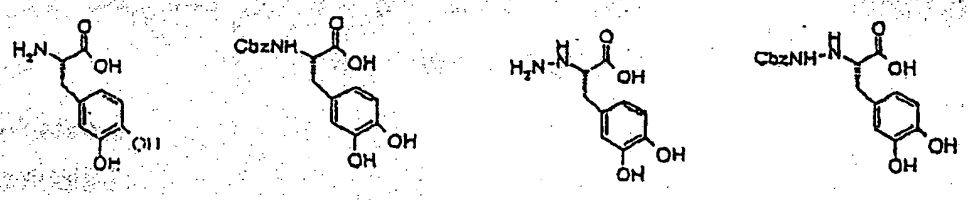


3-beta **CCCX**
3-alpha **CCCXI**



3-beta **CCCXII**
3-alpha **CCCXIII**

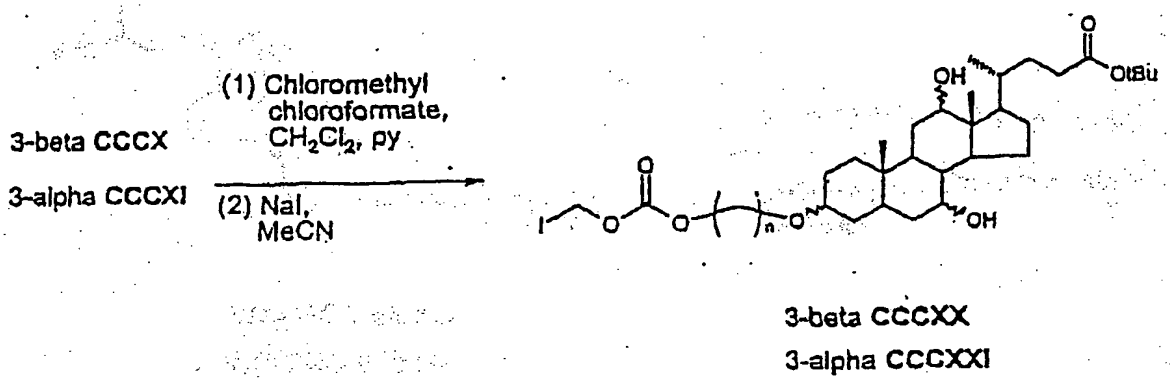
where D''-COOH is L-DOPA or carbidopa; and D'''-COOH is L-DOPA or carbidopa with an amino group protected with Cbz.



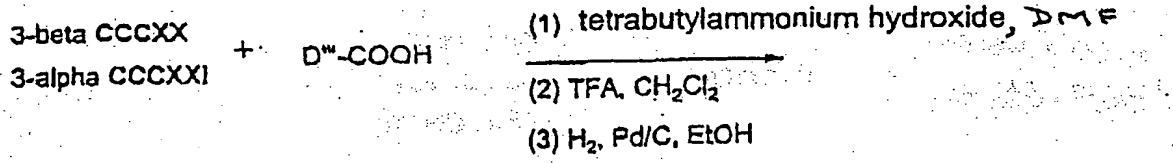
L-DOPA | Amino-protected L-DOPA | Carbidopa | Amino-protected carbidopa

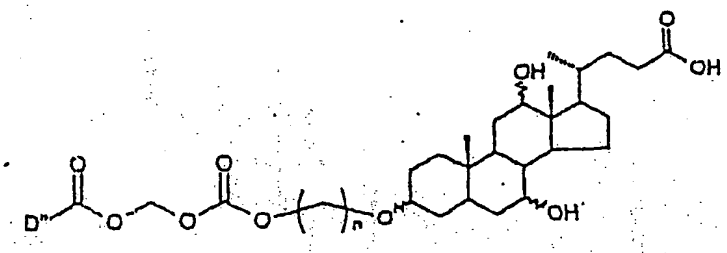
Scheme 4

FIGURE 31



3-beta CCCXX
3-alpha CCCXXI



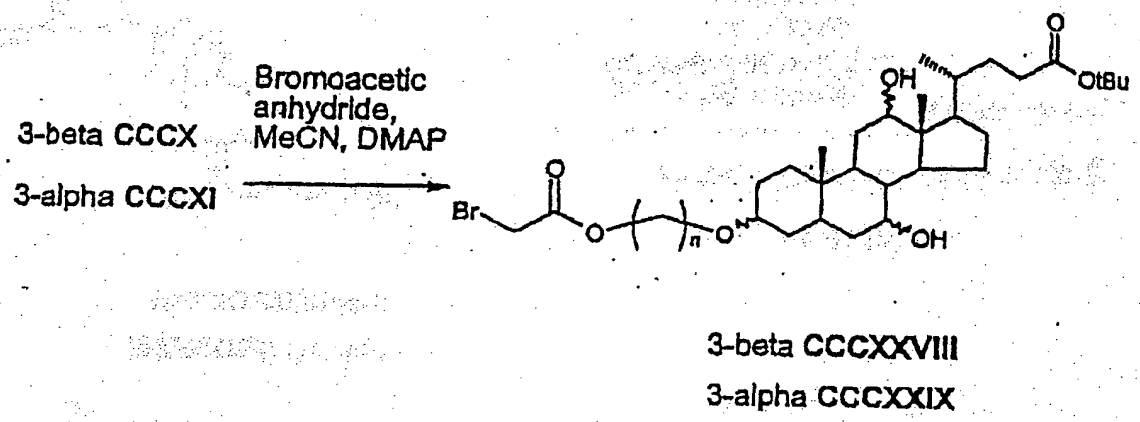


3-beta CCCXXII
3-alpha CCCXXIII

where D''-COOH is L-DOPA or carbidopa; and D'''-COOH is L-DOPA or carbidopa with an amino group protected with Cbz.

Scheme 6

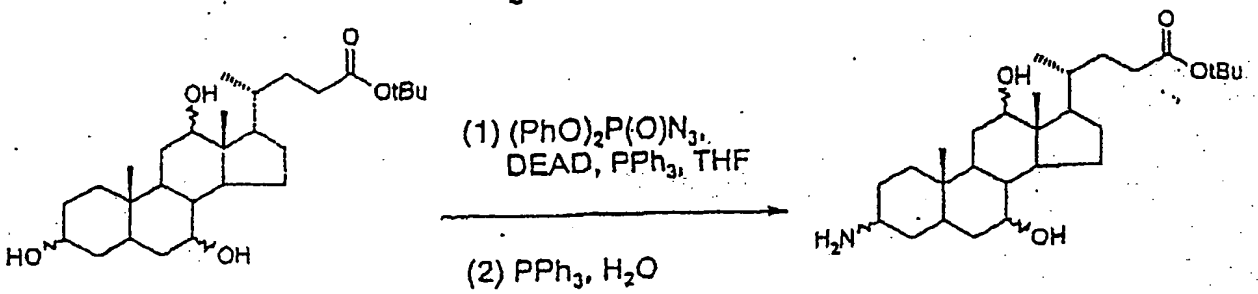
FIGURE 33



where D"-NH_2 is L-DOPA, carbidopa or benserazide.

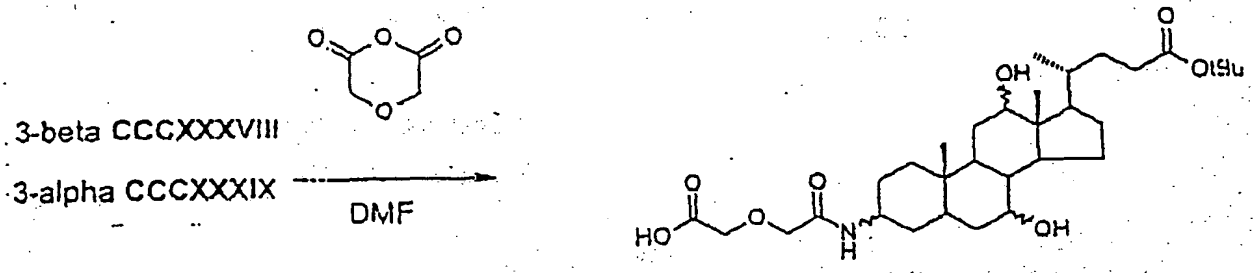
Scheme 8

Figure 35

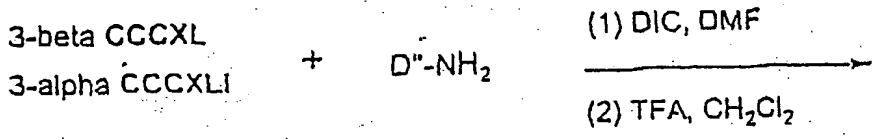


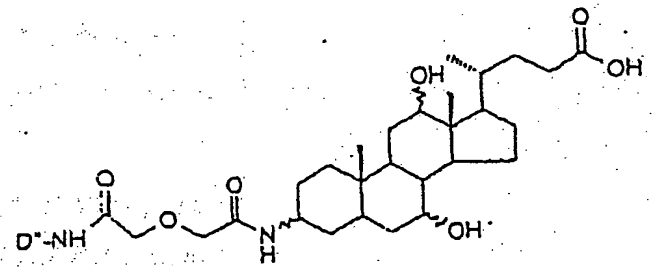
3-beta CCCXXXII
3-alpha CCCXXXIII

3-beta CCCXXXVIII
3-alpha CCCXXXIX



3-beta CCCXL
3-alpha CCCXLI



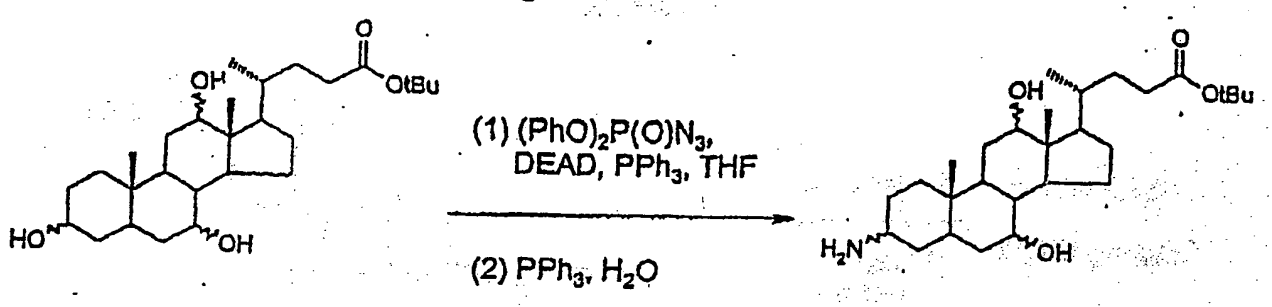


3-beta CCCXLII
3-alpha CCCXLIII

where D"-NH_2 is L-DOPA, carbidopa or benserazide.

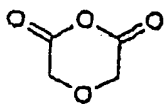
Scheme 10

Figure 37

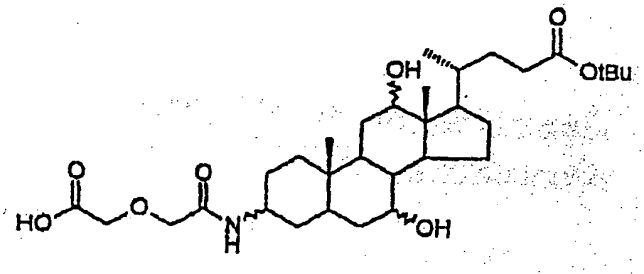


3-beta CCCXXXII
3-alpha CCCXXXIII

3-beta CCCXXXVIII
3-alpha CCCXXXIX



DMF

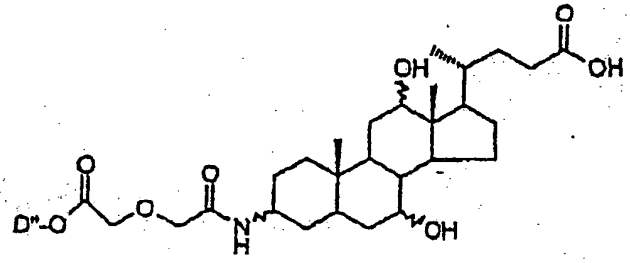


3-beta CCCXL
3-alpha CCCXLI

3-beta CCCXL
3-alpha CCCXLI

\+ D"-OH

(a) DCC
(b) $B(OH)_3$, H_2SO_4
(c) polyphosphate ester, DMF
(d) PPh_3, CCl_4, Et_3N



3-beta CCCXLVI
3-alpha CCCXLVII

where D"-OH is L-DOPA, carbidopa, benserazide, entacapone, nitecapone or tolcapone; reagents (a), (b), (c) and (d) are alternative reagents for the formation

Figure 39 - Synthesis of Cholyl-Dopa Conjugates

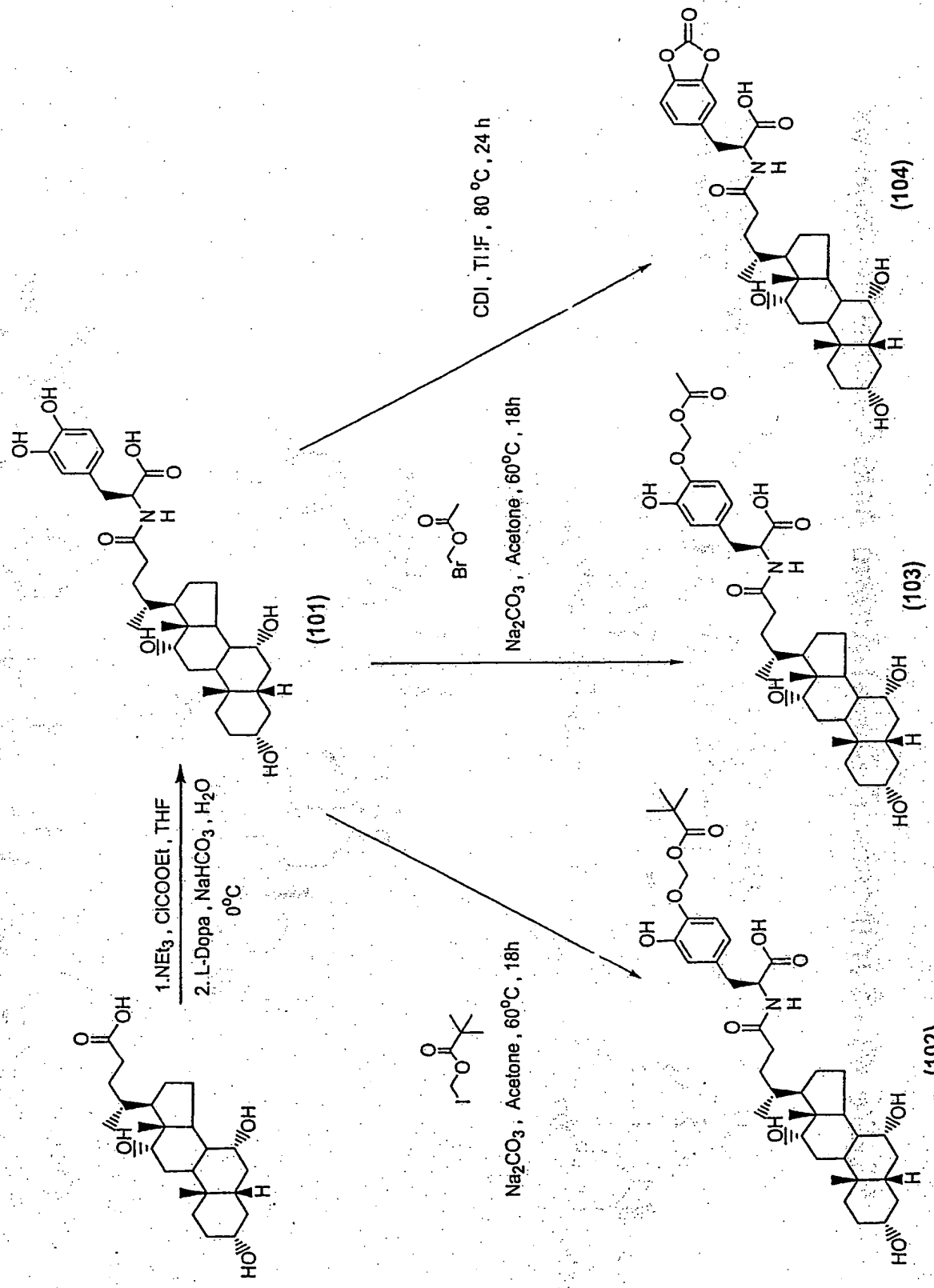


Figure 41 - Synthesis of Cholyl-L-Dopa Ester Conjugates